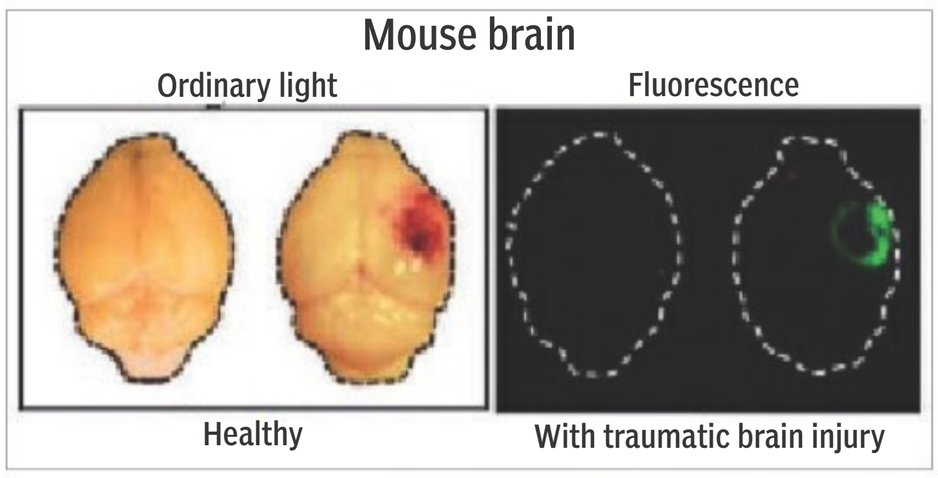
Guiding friends through the barrier

THE PROTECTIVE ARMOUR THAT SAVES THE BRAIN FROM HARMFUL THINGS ALSO PREVENTS THE ENTRY OF CURATIVE AGENTS, WRITES **S ANANTHANARAYANAN**

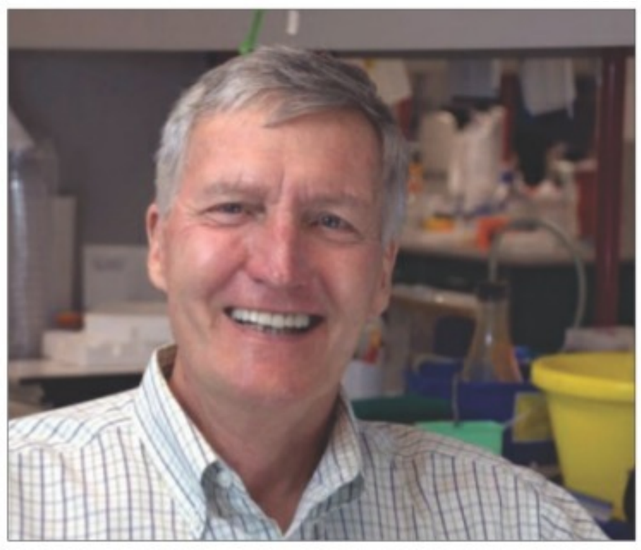


The blood vessels that serve the brain are lined with closely packed cells that prevent all but gases like oxygen and vital things like water and glucose from getting in. The trouble is that this barrier also keeps out any drugs that need to get there when there is an injury. The current treatment of brain injury or other diseases is, hence, limited to passive maintenance or invasive therapy that has its own drawbacks.

Aman P Mann, Pablo Scodeller, Sazid Hussain, Jinmyoung Joo, Ester Kwon, Gary B Braun, Tarmo Molder, Zhi-Gang She, Venkata Ramana Kotamraju, Barbara Ranscht, Stan Krajewski, Tambet Teesalu, Sangeeta Bhatia, Michael J Sailor and Erkki Ruoslahti, from different institutes of science and medicine in California, Massachusetts and in Estonia, report in the journal *Nature Communications* that they have developed a method of getting drugs through the shield and right where they are needed. They report that they have found a molecular sequence that zeroes in just where the brain has been injured and could thus form the vehicle to transport drugs that could limit the damage.

The brain needs a huge supply of energy and oxygen to keep working and the body provides this by generous blood supply. The adult brain gets about three quarters of a litre of blood every minute and this is 15 per cent of all the blood that the heart pumps out. Such a large consumer of blood also needs blood that is reasonably free from impurities and toxins. As the function of the blood is to move to and from the whole body, a variety of substances, including wastes, it ends up with a load of larger molecules that include toxins and bacteria. The blood vessels in most parts of the brain are thus provided with a lining that only allows oxygen, water and essential nutrients like glucose and some amino acids to diffuse through and does not allow normal exit and entry that is possible through blood vessels in other parts of the body.

This feature, which separates the circulating blood from the fluid around the cells of the brain, is called the *blood-brain barrier* and protects the brain from most pathogens. Infections of the brain that come through the blood are thus very rare. The antibodies that the immune system create are too large to cross the blood-brain barrier and only certain antibiotics are able to pass. The few infections that do occur are, hence, difficult to treat. In some cases, drugs are injected directly into the cerebrospinal fluid, where they can enter the brain, but this is neither possible nor effective most of the time. The procedure is also risky as it amounts to physically violating the security arrangement that has been set up specifically to keep toxins out.


Erkki Ruoslahti from the Sanford-Burnham Bregys Medical Discovery Institute, California.

There is, hence, no way of actively treating acute brain injury, the authors of the *Nature Communications* paper say, and the prognosis is poor. *Traumatic Brain Injury*, as such injury is known, the authors say, is termed a "silent epidemic" and it is a major cause of disease and death in children, teens and active adults till the age of 44. In certain cases, they say, disease or injury does cause a breakdown of the blood-brain barrier, which could allow entry of large molecules or drugs via the blood circulation. The entry alone of drugs, however, is not good enough as they diffuse and do not stay at the place of injury, the authors say.

Marking the site of injury

As a way to overcome this problem of getting the therapeutic agent to the site of damage, even when the blood-brain barrier had been pierced, the authors recall that they had earlier used a method to detect specific molecular signatures at places of injury to tissue. The way cells, proteins and viruses communicate is with the help of indentations on their surfaces. Proteins are long sequences of several of the 20 types of building blocks called amino acids. A virus infected with the coding for a short length of protein would display a specific pattern and attach to cells that have a structure that matches the pattern of the amino acid sequence that the virus expresses. If there is a library of viruses treated with different amino acid sequences, the pattern that corresponds to the cells affected by a particular virus can then be found out.

Using this method, the researchers had found that many injury sites displayed an affinity to specific amino acid sequences. The same thing should be possible at the site of injury within the brain, where specific changes in the molecular environment had been observed, they reasoned. Accordingly, they set out to see what chain of amino acids, or scrap of protein, may correspond to the molecular changes at the site of brain injury, so that a means of using this information to direct drug delivery could be devised.

The method used was to create puncture wounds to the right hemisphere of the brains of experimental adult male mice. This caused a rupture of the blood-brain barrier and antibodies in the blood leaked into the mass of brain tissue. Six hours later, a library of probe viruses marked with different scraps of amino acid sequences was injected into the blood stream of the mice. Thirty minutes later, when the extent of viruses present in the brain was assessed, it was found to be mostly in the right hemisphere, showing that it was there that the barrier had been pierced. And of the kind of viruses present, it was found that the ones marked with a particular four-amino acid sequence — *CAQK*, for *Cysteine, Alanine, Glutame* (denoted as "Q") and *Lysine* (denoted as "K") — were the ones that had remained at the injury site. As CAQK appeared to seek out and remain at the injury site, it looked like this four-amino acid sequence could be used to guide therapeutic substances.

As a control test, the CAQK amino acid chain that had been marked with a fluorescent label was injected, and it was found that the injured part of the brain lit up with fluorescence. Further tests, with injury to other organs like the liver or the skin, showed that homing of CAQK was specific to brain injury. CAQK homing was seen to be there even five days after the injury, which suggests that CAQK could be used to target the place of injury continuously for a period. And it was seen that accumulation of CAQK remained in place a good three hours after the injection.

Further trials using silver nanoparticles that had been treated with CAQK also showed that these nanoparticles accumulated at the injury site, just like the virus probes. Payloads of bits of DNA were also guided to the injury spot in the brain, with no accumulation at other, normal areas. And, finally, testing with sections of tissue from human brains showed that CAQK behaved in the same way with injured human brain tissue too. "These findings present an effective targeting strategy for the delivery of therapeutics in clinical management of acute brain injuries," the authors say in the paper.

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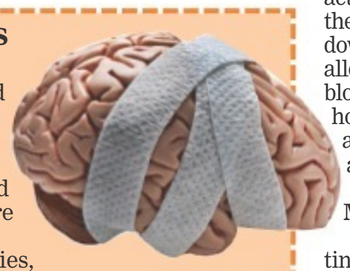
Vital statistics



Traumatic brain injuries are estimated to cost $76.5 billion a year. More than 1.7 million are believed to occur each year and 75 per cent of them are concussion. While 1.4 million are emergencies, 275,000 need hospitalisation and 52,000 result in death. The common causes are falls (35 per cent), car accidents (17 per cent), collisions (17 per cent) and assaults(10 per cent).

ORDERED EXTERMINATION

TAPAN KUMAR MAITRA EXPLAINS THE MECHANISMS BY WHICH RODENT POPULATIONS ARE CONTROLLED

The microbiological method of controlling harmful rodents is based on the artificial infection of the animals with pathogenic micro-organisms. Practical use has been found of bacteria from the genus *Salmonella*, which are pathogens of typhoid diseases in rodents. Cultures of the first two species — *Salmonella typhi spermophilorum* and *Salmonella decumanicidum* — were separated from ailing rodents (gophers and brown rats) during a natural epizooty at the end of the 19th century. The bacterium of *Salmonella typhimurida rodentia* was obtained experimentally after the multifold passage of strains of the bacillus *coli communis* on a conventional nutrient medium.

The artificial infection of rodents at their places of concentration may lead to the setting up of prolonged sites of infection. In favourable conditions, epizooties may develop on treated and adjacent sections. The contact of healthy specimens with ill ones is of paramount importance for the development of an epizooty. With considerable isolation of rodent habitats and diminishing contact between them, the possibility of infection on a large scale decreases.

It has been established that with the aid of bacteria like *Salmonella decumanicidum* which is the main ingredient of bactorodencide, artificial sites of epizooties can be set up in places inhabited by the common vole. Such an artificially induced epizootic process does not last long and in one or two months it attenuates because the main part of the population involved in the epizooty dies, while the remaining animals acquire an increased resistance to the pathogen. It has been established that rodents have a special mechanism of immunity to bactorodencide. A major role in protecting rodents' organisms from pathogenic bacteria is played by lysozime and similar substances present in the blood, liver, spleen, and other internal organs. On some bacteria, lysozyme has a bactericidal action, on others, a bacteriostatic action, while on third ones, it acts as a mutagen.

Bacterial agents do not put rodents on their guard and are readily eaten by them with food bait. When ingested with food, the bacteria act on the thin section of the intestine and the spleen. From three to 20, and sometimes up to 30 days elapse from the instant of infection to the appearance of the first symptoms of the disease.

The active ingredient of the rodent typhus relating to the genus *Salmonella* is bactorodencide and it is available in two formulations. The granular variant consists of grains with bacteria dried on them and the formulation must be stored in dry premises away from toxic substances. The storage period is one year at a temperature from -25 to +22 °C and three years from -25 to +4 °C. Dry aminobone bactorodencide has the form of a coarse-grained loose grey substance. Its moisture content is 6 per cent and its titre is at least 100 million.

The granular formulation is used against common and bank voles, and the aminobone formulation is used against common, bank, water voles, house mice, black and grey rats. Both formulations give the best results in the early or late spring when the rodents gather in separate places. The dose of granular bactorodencide depends on the species, number of rodents, and the kind of habitat treated.

Before applying the dry aminobone bactorodencide, it is subjected to reactivation for restoring the vital functions of the bacteria contained in it. For the purpose, warm (30-35 °C) boiled water is added to the formulation 10 to 12 hours before use in the ratio of 1:1. During that time, the wet substance is stirred two or three times and kept in warm premises. In the course of reactivation, the titre reaches 8,000-10,000 million. After reactivation, the formulation is mixed well with a double amount of bait (flour, groats, crushed grain, finely minced vegetables, potatoes, et al). The prepared bait is placed in the burrows, near the animals and along the paths used by them. The granulated aminobone formulation is used without bait and is not reactivated. The dose of the dry formulation for infecting one mouse or vole is 0.1-0.2 grams, and one rat, is 0.3-0.5 g.

In controlling mice and voles on fields, pastures, meadows, and in gardens, the rate of use of the powdered formulation is 100-200 g/ha, and of the granulated one is 250-500 g/ha. The control of these rodents in stacks of grain and the like requires 0.5- one g/m^3 of the powdered or one to five g/m^3 of the granulated formulation. In hotbeds, stores, livestock farms, and dwellings, the powdered formulation is used at a rate of 0.05 to one g/m^2, and the granulated one at a rate of 0.1to one g/m^2.

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Text scams ~ how to spot them

MOBILE PHONES ARE INCREASINGLY BECOMING THE MOST IMPORTANT PART OF PEOPLE'S WORK AND SOCIAL LIVES – WHICH MEANS THEY'RE MORE AND MORE VULNERABLE TO ATTACK, SAYS **ANDREW GRIFFIN**

The next text message you receive could ruin your life. Increasingly, SMS messages are being used as a way of duping people into giving up their online accounts and identities. Many of those messages arrive looking perfectly innocent, and even useful. But they could be incredibly dangerous — so it's important to make sure to know how to spot them.

One of the major problems with such scams is that it is now relatively easy to pretend to be someone else, over text. The technology that powers texts allows people to put custom names in when they send messages — allowing people to easily pretend to be Google, Apple or anybody else. As such, the main thing is to never give any information over text message, and only use it as a way of showing alerts. You never know who is texting you, or who you are texting — so treat it with extreme caution. One of the more recent scourges coming over SMS are iCloud scams. They aim to trick people into giving up the password they use to get into their Apple account — and, once hackers are into that, then they can easily get your bank account details, your location and more scary stuff besides.

Most of these notifications just work like traditional phishing scams, where cyber criminals pretend to be a company so that users send them details. But because they are done through the very personal but notoriously sketchy technology of SMS, they can be easy to spot.

It isn't clear why there has been such a huge amount of these in recent months but reports of them definitely do seem to be surging. The advice is the same as traditional phishing: responsible companies will never ask you to reply to a message with your personal details, or tell you to click on a dodgy link, so make sure that you always only give your information to official websites and be careful that you are.

Another more new development is tricks that try and get around the two-factor authentication that many products now have built in — and which, for the most part, serves as a big problem for people breaking into your account. That's why it's also become such a security risk.

Two-factor authentication works by attaching a phone number to a person's account. When they try to log-in, it will send a unique code to that phone number, and that has to be typed into the site. It's built to foil people who steal passwords and then use them to get into accounts, because it requires physical access to the phone; and that's why people are now trying to get around it with scams.

One highlighted this weekend showed a message that claimed to be from Google and told people that their account may have been hacked. If they wanted to have it shut down, it said, they needed to reply to the message with the six-digit verification code that they were about to receive.

It's a sneaky way of getting people to put the authentication message that they have received from Google into a text message so that scammers can get around the security set-up. But it's a curiously convincing one.

Again, the key is never to enter any important codes into a text message or any unverified sites. And sites such as Google and others that use two-factor authentication will only ever send you the messages if you ask for them; if you're receiving them without asking, it probably means someone is trying to break into your account.

THE INDEPENDENT

PLUS POINTS

Life after death?

"Is there life after death?" is a question that has dominated human thinking since time immemorial. But now researchers have discovered that an animal's genes can "live" on for up to four days after its body has died, according to a report in *Science Magazine*. And some genes, including ones that help to create an embryo and others associated with cancer, even turned on or became more active after death.


Genes in dead zebrafish were found to remain active for up to four days.

The research could potentially help reduce the increased risk of getting cancer after transplant and also help forensic scientists work out when a murder victim was killed. One of the scientists, Professor Peter Noble, of Washington University in Seattle, said the study was "an experiment of curiosity to see what happens when you die. We can probably get a lot of information about life by studying death".

The researchers studied what happened to more than 1,000 genes in mice and zebrafish after they died. Changes in their genes were recorded for up to four days after death in the zebrafish and for two days in the mice. "We initially thought that sudden death of a vertebrate would be analogous to a car driving down a highway and running out of gas. For a short time, engine pistons will move up and down and spark plugs will spark — but eventually the car will grind to a halt and die," the researchers wrote in an article on the bioRxiv website.

"Yet, in our study we find hundreds of genes are upregulated many hours post-mortem, with some upregulated days after organismal death. Since the post-mortem upregulation of genes occurred in both the zebrafish and the mice in our study, it is reasonable to suggest that other multi-cellular eukaryotes (forms of life) will display a similar phenomenon. What's jaw-dropping is that developmental genes are turned on after death," Professor Noble.

Promoting memory

Working out is good for the brain and a team of scientists from the USA and Germany now has a clearer idea why. A protein called cathepsin B, produced and secreted during exercise is required for exercise-induced memory improvement and brain cell production in mice, the scientists reported in *Cell Metabolism* on 23 June. They also showed that levels of cathepsin B were positively correlated with fitness and memory in humans.


New brain cells (green) are induced by exercise.

To hunt for muscle-produced factors called *myokines* that might modulate brain function, Henriette van Praag of the National Institute on Ageing and colleagues treated rat muscle cells in culture with the drug AICAR — "an exercise mimetic," explained van Praag, meaning it boosts the cells' metabolic activities. Among the proteins upregulated in the treated cells was a secreted factor, small enough to traverse the blood-brain barrier, that had previously been shown to be upregulated in muscle during exercise: cathepsin B.

In mice that exercised for two to four weeks, plasma levels of cathepsin B were significantly increased, van Praag's team found. And the animals showed improved memory as well as increased neurogenesis in their hippocampi — a brain region involved in learning and memory.

THE SCIENTIST

Finches & Parkinson's

Scientists have only recently begun to pin down the effect of a Parkinson's-like loss of dopamine in songbirds. Sam Sober and his colleagues at Emory University in Atlanta found that treating the basal ganglia of adult Bengalese finches (*Lonchura striata*) with the neurotoxin 6-hydroxydopamine, which destroys dopaminergic neurons, causes defects in vocal learning.

Previously, neurobiologists Stephanie White of the University of California, Los Angeles, and Julie Miller, now at the University of Arizona, found that 6-hydroxydopamine reduced vocal variability during undirected song, when the finches should have produced more-variable songs. People with Parkinson's also speak in a more monotonous tone, but how dopamine affects this symptom is unknown.

Current finch models of Parkinson's rely on neurotoxin-induced lesions in specific brain areas, not genetic mutations associated with the disease in people. Finch researchers have already begun to probe genetic models in another neurodegenerative disorder: Huntington's disease. Last year, scientists characterised a transgenic songbird with the mutant huntingtin gene that exhibited both tremors and repetitive, "stuttering" song patterns similar to deficits seen in the human disease.

THE SCIENTIST