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Toxic gases! Therapeutic? What?!

Carbon monoxide is a toxic gas – could it really be used as a treatment for disease?

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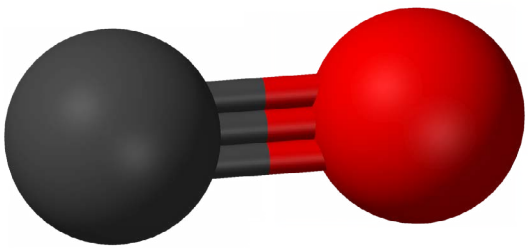
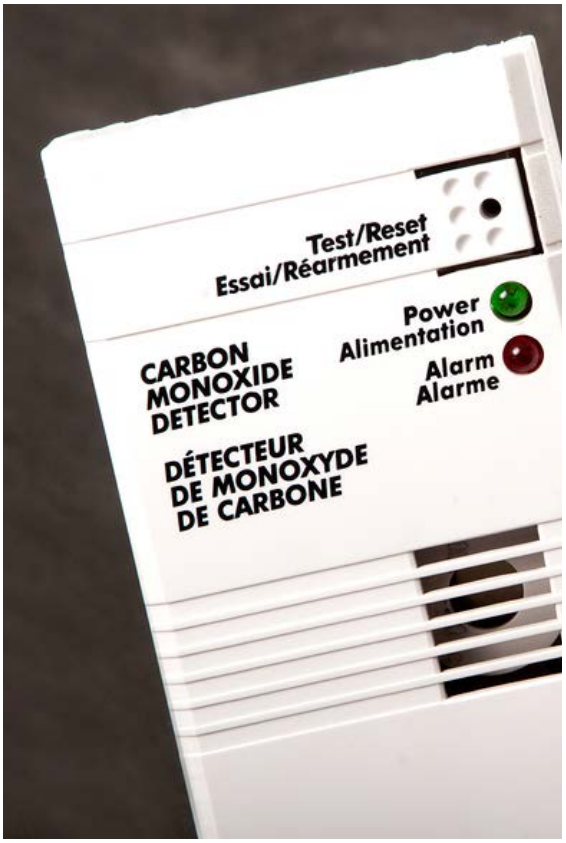
heart arrhythmia

Carbon monoxide (CO) is best known as a toxic gas but may one day be used as a therapy for difficult to treat diseases, as three scientists from the University of Reading explain.

Carbon monoxide is an odourless gas produced during the incomplete combustion of carbon, for example in faulty heating and gas appliances. Although carbon monoxide is rightly regarded as a highly toxic gas, it has been known since the 1890s that organisms generate CO within their bodies. CO can interfere with oxygen transport in the blood as it binds to the haemoglobin in red blood cells. However its main toxicity is believed to be due to its disrupting the function of the mitochondria.



Carbon monoxide molecules contain one carbon and one oxygen atom bonded together. It is more reactive than carbon dioxide.



Many homes have a carbon monoxide detector as the gas can kill.

What is now becoming apparent through exciting scientific research is that this gas could be a potential therapeutic treatment for many neurological (brain and nerve) diseases. As a result, scientists have been looking at the effects of low levels of CO in the body with the hope that CO could be a therapeutic remedy for complex and difficult to treat diseases such as Alzheimer's disease (AD).

CO in the body

Most research into how CO can help the body is focussed on enzymes called heme oxygenases. These enzymes are essential in the body and break down heme, which is part of the haemoglobin molecule which carries oxygen round the body. The heme is broken down to produce the chemical bilirubin, Fe^{2+} ions and CO. Ridding the body of heme is essential and organisms that lack the gene to produce heme oxygenase have a severely shortened life span.

In many age-related neurodegenerative diseases such as Alzheimer's, patients have an increased amount of heme oxygenase in the brain cells. An increased amount is also found when not enough blood reaches the brain, for example during a stroke. Research seems to suggest that the heme oxygenase enzymes protect the brain in event of a stroke, but it is not clear which of the products of breaking down heme provide that protection. The evidence is starting to point towards it being CO.

As you can imagine, finding out which of the products of the breakdown of heme provide protection to the brain is not an easy task, but it has been helped recently by the development of molecules which release carbon monoxide. These are called CO Releasing Molecules (CORMs) and can be given to patients, releasing CO at the required site in the body. At Reading University we are using these to investigate the role of carbon monoxide in the cardiovascular and nervous systems.

What we have uncovered is a tale of two systems and that what is good for the head is not good for the heart.

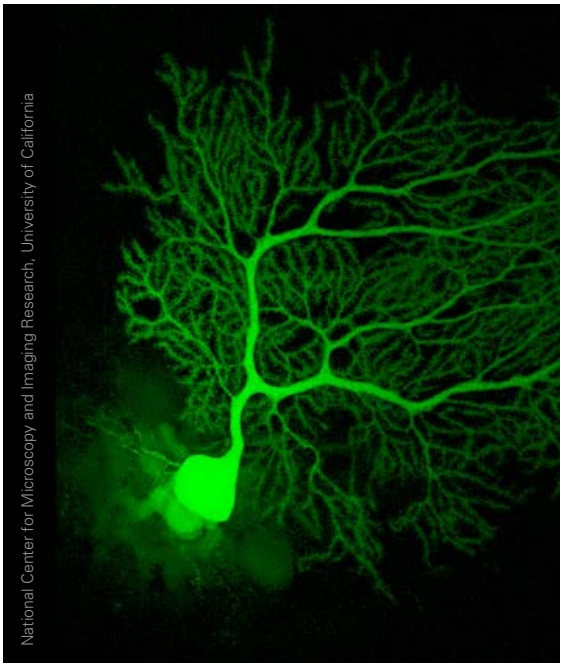
Tackling Alzheimer's

Alzheimer's disease (AD) affects some 820 000 individuals in the UK with no treatments currently available to prevent this disease. Our studies have revealed a surprising protective effective of carbon monoxide against the nerve cell death caused by AD.

The author Terry Pratchett died of Alzheimer's disease in March 2015. He donated a million dollars to research into the disease.

Previous research has shown that there are toxic proteins involved in the development of AD, one of which is called amyloid beta (Aβ) which causes nerve cell death. Our innovative experiments tested to see if CO could prevent it causing cell death. To our surprise, application of CO does prevent the cell death previously observed in the presence of Aβ. We tested our experiments in a range of experimental models and the result was consistent: CO prevented Aβ-induced cell death. While these are laboratory experiments it suggests that, in the case of Alzheimer's, CO could provide a novel therapeutic option.

This research is in support of previous work highlighting that CO protects nerve cells. Further research has shown that it is the brain's support cells (glia) which produce the CO which protects the nearby neurons.

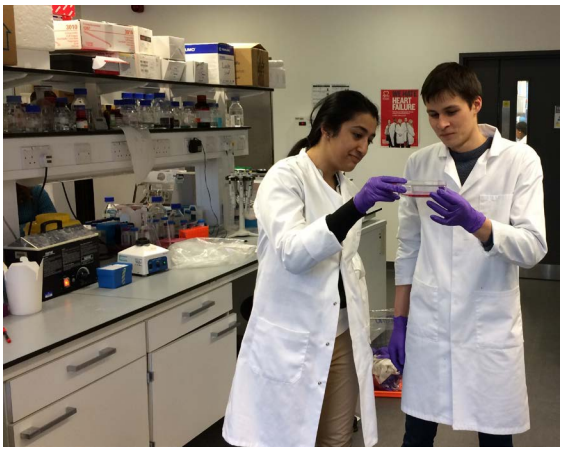


A neuron or brain cell, shown up using a fluorescent dye. Each one connects with many others forming a network in the brain.

CO and heart muscle

It has been known for some time that exposure to carbon monoxide from environmental pollution can lead to heart problems such as arrhythmia, which is irregular beating of the heart. This can occur through exposure to low concentrations of CO which are not enough to kill (30-200 ppm) and are therefore not often associated with CO poisoning. Until recently there was no scientific explanation for these effects.

We carried out studies both *in vitro* (in the lab or literally 'in glass') and *in vivo* (in living cells) to determine the effects of CO on heart muscle cells. Exposure to CO disrupted the normally regular heart rhythm.



Hafeeza Ayuoob (left) and Vytautas Kontrimas (right), two summer students looking at the effects of carbon monoxide on cultured brain cells.

Proteins known as ion channels are found on individual heart muscle cells and are essential for the coordinated beating of the heart.

Malfunctioning ion channels are the cause of many cardiac diseases. Through a series of experiments we showed that CO interacted with a sodium ion channel to change its function and produce arrthymias (irregular heartbeats). Further work showed that another gas, nitric oxide, was also involved in this damaging effect to the heart rhythm.

This is bad news for using CO to help the brain – it would not be wise to protect the brain but damage the heart while doing so. However, we have also found a drug which could alleviate the effects of CO on the heart. Ranolazine, a drug already prescribed for angina, prevented the irregular heart rhythms that were induced by CO. Therefore this could be used as a therapy for patients presenting with low level carbon monoxide exposure and cardiac complaints.

Next steps

While this research area is progressing at a rapid pace, more work is required. The next steps will be to conduct further experiments to test the functional effects of exposure to these gases and find the detailed mechanisms of how they have their effects. It is also necessary to examine the effects of these gases on the diverse cell types within the body.

It is interesting that an already approved drug prevented the effects of CO and it could be trialled in patients presenting with cardiovascular complications where it is thought that CO might be causing the problems. Firefighters, for example, have high exposure to CO over the course of their career and this might cause heart problems.

As we said above, although a lot more research is still required in order for a potential therapy to be produced, we can still speculate about how the gases could provide a promising future to patients with neurodegenerative diseases such as Alzheimer's. For a start, carbon-monoxide releasing molecules (CORMs) are widely used in current research projects and pharmaceutical companies are working on the next generation of compounds. There are fewer molecules that can be used to release H_2S in the body to observe its effects but research groups at the University of Exeter are tackling this problem.

Most recently, a medical device capable of delivering controlled amounts of CO has been investigated in controlled medical trials. This device is aimed at respiratory disorders such as asthma; however it would be logical to speculate that similar devices could be adapted as therapeutic options to slow down neurodegenerative diseases such as Alzheimer's disease in the future. We are therefore closer to using toxic gases for the treatment of complex diseases, which re-enforces Paracelsus's adage that 'the dose makes the poison'.

Dr Mark Dallas is a neuroscience lecturer at the University of Reading, UK; Hafeeza and Vytautas are third year Pharmacy students who spent the summer in Dr Dallas's lab.