Best in small doses

Sometimes a smidgen of toxin can be just what the doctor ordered, say biologists **Mark Mattson** and **Edward Calabrese**

"WHAT doesn't kill you makes you stronger" is a phrase often used to explain the resilience of people who have endured hardships. Like many aphorisms it contains more than a grain of truth. It describes the theory of hormesis – a process whereby organisms exposed to low levels of stress or toxins become more resistant to tougher challenges.

The theory of hormesis has been around for decades, but has long been met with scepticism or downright suspicion. In recent years, however, biologists have pieced together a clear molecular explanation of how it works, and hormesis has finally been accepted as a fundamental principle of biology and biomedicine. The question now is how to take advantage of hormesis to live longer and healthier lives.

The basic idea was first recognised in the 16th century by the Swiss physician and alchemist Paracelsus, who wrote that "all things are poison and nothing is without poison, only the dose makes something not a poison". The effect was first demonstrated experimentally in the 1880s when Hugo Schulz of the University of Greifswald in Germany observed that certain agents that inhibited yeast metabolism at high doses stimulated it at low doses. The word hormesis itself (from the Greek "to excite") was coined in 1943.

The defining characteristic of hormesis is the "biphasic dose response", in which high doses of a substance are toxic but low doses are beneficial (see diagram, page 39). This is very different to the two standard dose-reponse models used in toxicology, in which something is either assumed to be neutral up to a certain threshold or to act linearly, with toxicity directly proportional to dose (see "Toxicology's top model", page 38).

In fact, more toxins exhibit a biphasic response than a linear or threshold one, and biphasic responses have been reported in organisms ranging from bacteria to humans. For example, high doses of cadmium are lethal to snails and blowflies, yet small amounts can improve their reproductive capacity. Similarly, low doses of radiation increase the growth rate of plants and the lifespan of crickets and mice, but high doses are fatal. And chemicals that are carcinogenic when consumed in high amounts can inhibit the growth of cancer cells at low doses. Other hormetic "toxins" include arsenic and pesticides.

What is more, many compounds that improve health at low doses, including vitamin A, vitamin B6, selenium, iron and zinc, are toxic at high doses.

The biphasic response is not limited to exposures to environmental agents, though,

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it permeates all of biology. One example is the neurotransmitter glutamate, released into synapses when the brain is engaged in everyday activities.

Glutamate relays messages from nerve cell to nerve cell, but we now know that it also triggers low-level stress responses that promote nerve cell growth and survival (*Neuron*, vol 42, p 535). It is highly toxic to nerve cells at high levels, though, for example when excess amounts spill out into the synapses after brain injury.

So how can exposure to low levels of toxins or other stressors have beneficial effects? The answer lies in the squadrons of defence molecules the body calls up in response to threats. Once rallied, these molecules not only deal with the immediate threat but also increase resistance to other threats. They can even repair existing damage.

Heat shock

One such molecular defence force is the heat shock proteins. Produced when cells are exposed to high temperatures, toxins or inflammation, their job is to protect other proteins from damage by binding to them and shielding them from attack. Another bodyguard, sirtuin 1, senses cellular stress and activates battalions of genes that code for protective proteins such as antioxidants and cell-membrane stabilisers. Other bodyguards function as messengers that are released by cells under threat to alert other cells of the danger. Growth factors, for example, mobilise the defences of cells that are in danger but not yet under attack.

In some cases, the bodyguards not only protect cells and organs but also enhance their function. For example, growth factors released in the brain during exercise promote the growth of new nerve cells and synapses. The bodyguards can even reverse existing damage. A good example is growth factors that induce the proliferation of healthy cells in damaged tissue.

The body's molecular bodyguards evolved to protect us from naturally occurring threats, but there are ways to activate them deliberately. One is by eating lots of fruits and vegetables. There is plenty of evidence that a diet rich in plant material will help reduce your risk of cardiovascular disease, cancer and some neurodegenerative disorders. The standard explanation for this is that fruit and vegetables contain high levels of antioxidants such as carotenoids and flavonoids. These neutralise damaging chemicals, called free radicals, that are an unavoidable by-product of metabolism.

At first glance this makes sense, given that free radical damage has been implicated in cardiovascular disease, cancer and neurodegenerative diseases. However, most plant antioxidants only mop up free radicals at high concentrations that cannot be achieved by eating normal amounts of fruit and vegetables. Also, clinical trials of high-dose antioxidants have failed to show that they can prevent or treat these diseases.

So if not antioxidants, then what? Tellingly, antioxidants are part of a wider class of plant chemicals, called phytochemicals, that are toxic at high doses but beneficial at lower doses. These are probably natural pesticides that evolved to deter herbivores. The amounts we normally eat are insufficient to reach toxic concentrations in the human body, but are enough to activate our molecular stress responses. In other words they are hormetic stressors.

In some cases we know exactly how they work. Resveratrol, the chemical believed to be responsible for the health benefits of red wine, activates sirtuin 1, while sulforaphane from broccoli activates a protein called Nrf2, which switches on genes for antioxidant and detoxification enzymes. Nrf2 is also activated by curcumin from turmeric. Allicin (from garlic) and capsaicin (from chilli) also induce a mild stress response by directly opening pores in cell membranes called TRP ▶

Toxicology's top model

When it comes to assessing risks from chemicals and physical agents such as radiation, toxicologists have two tools in their boxes. The main one is the threshold model, which assumes that a toxin must reach a certain level before it causes harm. The other, used for carcinogens, is the linear model, which assumes that risk rises in direct proportion to dose.

Both models are severely challenged by hormesis. In head-to-head comparisons, hormesis far outperforms them in predicting the effect of various doses for most classes of chemicals and physical agents, especially at low doses. Yet toxicologists and the regulatory agencies that use their guidance continue to shun hormesis, and stick doggedly to the threshold and linear models.

In part this is a matter of convenience. It is a lot easier to recommend eliminating a "toxin" from the environment, or at least minimising exposure to it, than to recommend exposure to lower, beneficial, doses.

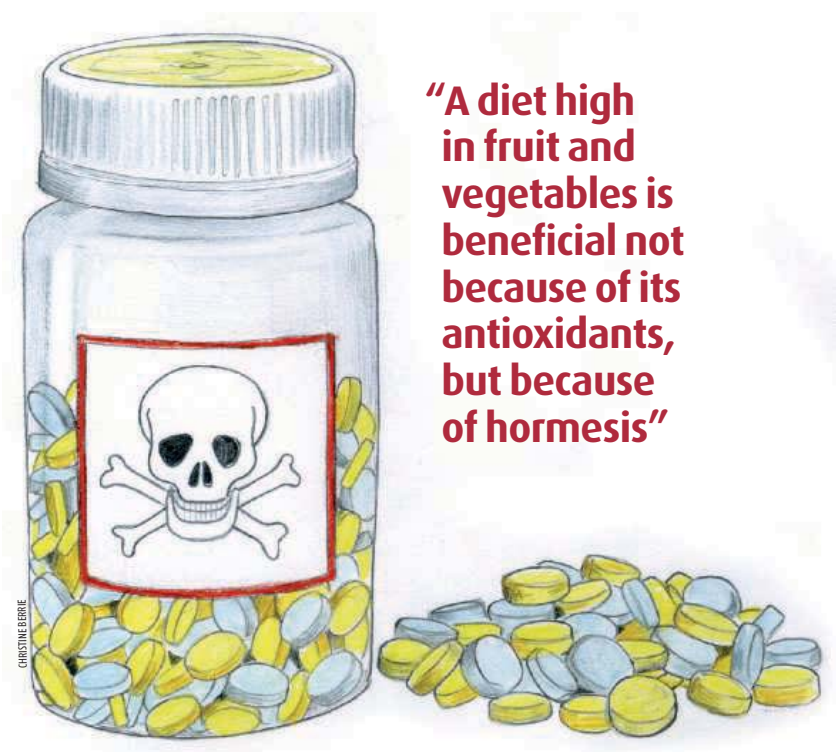
It is our belief that the hormetic model should become the default in risk assessment. Exactly how this would affect environmental standards remains to be seen, but a first step would be for an impartial panel of scientists to evaluate the hormetic dose response model and its comparison with the other two models.

channels. This causes an influx of calcium which drives the production of growth factors. Based on this evidence, we believe that a diet high in fruit and vegetables is beneficial not because of its antioxidants, but because of hormesis.

Recent research has also shown that hormesis is responsible for at least some of the health benefits of exercise and calorie reduction. Reducing calorie intake and increasing energy expenditure lowers your risk of diabetes and cardiovascular disease, and we now know this is because diet and exercise induce a state called "mild metabolic stress", where levels of glucose and the molecular energy currency, ATP, are depleted. Cells respond to this by activating stress-response pathways that increase their ability to take up glucose in response to insulin. This hormetic reaction is, in part, why exercise and dieting help prevent diabetes (*Mechanisms of Ageing and Development*, vol 126, p 913).

Mild metabolic stress also causes cells in the heart and gut to produce proteins that decrease heart rate and blood pressure and increase gut motility, reducing the risk of heart disease, stroke and colon cancer.

Even just cutting back on calories is beneficial. Research at one of our laboratories has shown that feeding rats and mice only every other day improves the health and function of their brains, hearts and other organs (*Journal of Nutritional Biochemistry*, vol 16, p 129). Other researchers have shown that mice and rats on similar feeding regimes develop fewer cancers, are less prone to neurological disorders and live 30 per cent longer than their siblings that were fed every day. Metabolic stress is important for these effects.



"A diet high in fruit and vegetables is beneficial not because of its antioxidants, but because of hormesis"

Hormesis also benefits the brain. Studies of human populations have shown that dietary restriction and regular exercise reduce the risk of Alzheimer's and Parkinson's, a link that is backed up by animal studies. In animal models of Alzheimer's, diet and exercise decrease the deposition of amyloid protein "clots" in the brain, while in mouse and monkey models of Parkinson's they prevent the degeneration of dopamine neurons, the hallmark of the disease.

It is also possible to make the brains of rats and mice more resilient to stroke damage by exposing them to a brief bout of high temperature or restricted blood flow prior to the stroke. These stressors trigger the production of heat-shock proteins and growth factors, which enhance the ability of the neurons to ride out the stroke.

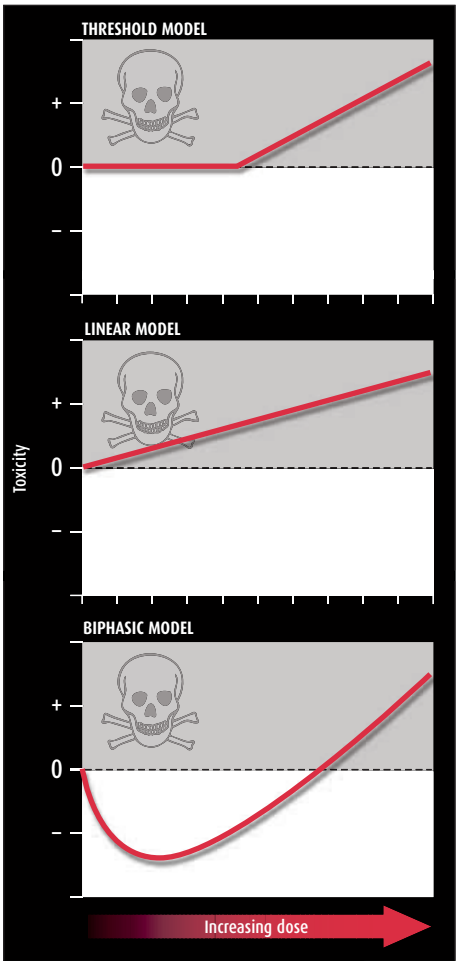
Use it or lose it

Dietary restriction and exercise may even enhance brain function in healthy individuals. Learning and memory improve in rats and mice that exercise regularly or eat low-calorie diets, and exercise and diet have been shown to boost cognitive function in humans.

It is also possible to enhance your brain function simply by keeping mentally active. Intellectually challenging occupations reduce your risk of developing neurodegenerative

A LITTLE BIT OF WHAT YOU FANCY

Poisons are generally assumed to act in direct proportion to their dose, either above a threshold (top) or from the start (middle). In reality, most show a biphasic curve, where low doses are beneficial (bottom). This is the basis of the theory of hormesis



disease because of the beneficial stress imposed on active neurons. The mediator here appears to be glutamate, which activates energy production by mitochondria and hence free-radical production. These stressors result in the activation of protective molecules such as antioxidant enzymes.

Exercise, dietary restriction and intellectual challenges also produce changes in the structure of the nerve cells themselves, increasing the number and size of synapses to enhance their information-processing capacity. Neuroscientists have even discovered that regular excitation of nerve cells is required for their survival; neurons that don't fire die.

Mild stresses can also stimulate stem cells in the brain to divide and form new neurons. An understanding of neurogenesis is leading to the development of new drugs and dietary supplements to promote the replacement of neurons damaged through injury or disease. Epicatechins, present in cocoa and green tea, are a promising candidate (*Journal of Neuroscience*, vol 27, p 5869).

Another recent discovery is that some commonly prescribed drugs may work through hormesis. An example is the SSRI class of antidepressants, such as fluoxetine (Prozac) and paroxetine (Paxil). At high doses these drugs are toxic, but at low doses they stimulate nerve cells to produce BDNF – brain-derived neurotrophic factor – a protein that promotes the growth and survival of neurons in the hippocampus, a brain region critical for learning and memory. A lack of neurogenesis in this region is widely believed to be a major cause of depression (*Behavioral Pharmacology*, vol 18, p 391).

The diabetes drug metformin may act, in part, by inducing mild stress in muscle cells similar to that caused by exercise. Both exercise and metformin stimulate the activity of a protein called AMPK, which increases the sensitivity of muscle cells to insulin.

The fact that drugs act by hormesis has implications for the way they are used. Dose is obviously critical when deciding whether a stressor is beneficial or damaging, but so too is timing. Just as with exercise, cells must have time to recover in order to accrue the benefits of stress. During the recovery period, any cell damage caused by the stress is repaired, and the cells also increase their production of stress-resistance proteins.

However, the standard approach in pharmacology – also applied to dietary supplements – assumes that drugs are most effective when kept at a constant concentration in the body. This need not apply to drugs that act by hormesis, which may be most beneficial when delivered intermittently. So a major goal of pharmacology should be to find not just the most effective dose of drugs, but also the ideal frequency of administration.

Although the potential of hormesis to prevent and treat disease is becoming clear, it remains largely untapped. To make the most of what we now know, we need to identify hormetic agents, work out how they affect general health and specific diseases and look into their possible additive benefits.

There is progress. We have developed tests to detect the activation of hormetic stress responses in cultured cells and tissues, and are now using these tests to screen hundreds of chemicals isolated from plants and micro-organisms to identify potential hormetic agents. Once a new candidate has been identified, we test it for its ability to protect against diseases such as diabetes, cancer and neurological disorders. Pharmaceutical companies and the natural products industry are increasingly aware of the potential of hormesis.

There has perhaps been too much emphasis on the unhealthy aspects of stress, on the assumption that all types of stress are bad. But as research like ours reveals, depending upon its quantity and duration, stress can improve the length and quality of life. We expect that this expanding knowledge will generate a menu of "good stressors" for us to incorporate into our daily lives. ●

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Further reading: "Hormesis: Why it is important to toxicology and toxicologists" by Edward Calabrese, *Environmental Toxicology and Chemistry*, vol 27, p 1451; "The Importance of Hormesis to Public Health" by Ralph Cook and Edward Calabrese, *Environmental Health Perspectives*, vol 114, p 1631.