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Author manuscript

*Sci Am.* Author manuscript; available in PMC 2018 March 07.

Published in final edited form as:

*Sci Am.* 2015 July ; 313(1): 40–45.

## WHAT DOESN'T KILL YOU...

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### Abstract

Chemicals that plants make to ward off pests stimulate nerve cells in ways that may protect the brain against diseases such as Alzheimer's and Parkinson's

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When asked why eating lots of fruits and vegetables can improve health, many people will point to the antioxidants in these foods. That reasoning is logical because major diseases such as cancer, cardiovascular disease and diabetes involve cell damage caused by chemicals called free radicals that antioxidants neutralize.

As a neuroscientist working to understand what goes wrong in the brain, I have long been aware that free radicals disrupt and sometimes kill neurons. And conversely, I know that people who regularly consume vegetables, fruits and other plant products thought to contain high levels of antioxidants tend to have healthier brains and to be less likely to suffer from neurodegenerative diseases. But the antioxidants story is not quite so simple.

Indeed, when rigorously evaluated in controlled trials in animals and humans, antioxidants, such as vitamins C, E and A, have failed to prevent or ameliorate disease. How then do fruits and vegetables promote health?

The emerging answer has much to do with the strategies that plants have evolved over millions of years to protect themselves from pests. Bitter-tasting chemicals made by plants act as natural pesticides. When we eat plant-based foods, we consume low levels of these toxic chemicals, which mildly stresses cells in the body in much the same way that exercise or going without food for long periods does. The cells do not die—in fact, they get stronger because their response to the stress shores up their ability to adapt to still more stress. This process of bolstering cellular resilience is called hormesis—and a growing body of research indicates that it accounts for the health benefits of consuming fruits and vegetables. Understanding hormesis's effects may even provide new ways to prevent or treat some of the most devastating brain diseases, including Alzheimer's, Parkinson's and stroke.

## STRESS IS GOOD

My colleagues and I have collected some of the data on hormesis in the brain after coming to the work somewhat circuitously. In the early 1990s my team, then at the Sanders-Brown Center on Aging at the University of Kentucky, set out to investigate whether antioxidants could provide a treatment for Alzheimer's. We thought they might be helpful because we had seen beta-amyloid—the pernicious protein that accumulates excessively in the brains of Alzheimer's patients—wreaking havoc on brain cells in culture and knew that free radicals were involved in the destructive process. Unfortunately, when tested at various medical

centers in a clinical trial led by Douglas R. Galasko and Paul Aisen, both at the University of California, San Diego, high doses of antioxidants had no benefit in Alzheimer's patients. We then shifted our efforts to a seemingly different problem, which serendipitously led us to develop a new hypothesis of why eating plant foods is good for brain health.

We and others had noted that people who exercise regularly, eat relatively few calories and experience a variety of intellectual challenges tend to maintain a higher level of brain functioning than people with the opposite way of life. They are less likely to suffer from Alzheimer's, Parkinson's or stroke. We wondered whether diet, exercise and intellectual activity influence brain function and disease susceptibility by affecting the same molecular processes in brain cells.

Beginning with a study in 1999 by Annadora Bruce-Keller, then a postdoctoral fellow in my laboratory and now a professor at Louisiana State University's Pennington Biomedical Research Center, we found that the neurons in the brains of rats on an alternate-day fasting diet were resistant to neurotoxins known to cause symptoms that mimic epilepsy and Huntington's disease, whereas normally fed animals succumbed to the chemicals. Shortly thereafter, I was recruited to head the Laboratory of Neurosciences at the National Institute on Aging, where our research found that fasting every other day also protects the brain in animal models of Alzheimer's, Parkinson's and stroke.

As we worked to understand why fasting was good for the brain, it became clear that neurons were responding to food deprivation by mobilizing molecular defenses against free radicals and the accumulation of beta-amyloid. The defense systems entailed producing proteins known as neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), that are critical for neuron survival, as well as proteins that bolster efficient use of energy and prevent the accumulation of damaged molecules.

From an evolutionary standpoint, the demonstration that fasting intermittently can be beneficial should not be overly surprising. It creates a mild stress that puts the brain into a state where the protection of neurons is paramount, which would allow the animal to function at a high level and obtain food even when it is in short supply and the animal has to expend energy to find it.

Our interest in the beneficial effects of stress on brain cells eventually led us to look at the neurological effects of plants in the diet. We were intrigued by reports in journals during the 1970s that a neurotoxin in seaweed, called kainic acid, was able to bind to and cause excessive activation of receptors on the surface of brain cells that serve as docking sites for glutamate, the main signaling molecule that switches on neurons.

Our group and others had already demonstrated the paradoxical effects of glutamate in fasting and exercise. Too much stimulation of the receptors can damage or destroy neurons. More moderate activation of these receptors, however, turns on a chemical pathway in neurons that plays a critical role in learning and memory and in protecting neurons. Such discoveries began to raise the question of whether low levels of plant neurotoxins in fruits and vegetables might yield beneficial health effects by inducing similar mild stresses in brain cells.

## “DANGER, WILL ROBINSON!”

The health benefits of fruits and vegetables are an inadvertent off-shoot of eons-long wars waged by plants against critters, mostly insects, that are intent on eating them. To survive as individuals and species, they had to develop ways of preventing their own extinction. Over the course of hundreds of millions of years of evolutionary history, they came to produce natural pesticides.

These chemicals usually do not kill the insects: a plant does not care whether predators die; it just wants them to go away and not come back. One common way that plants send pests packing is targeting their nervous systems. The plants produce chemicals that act on neurons called sensilla in the bugs' mouthparts, which are similar to the taste bud cells in the human tongue. Signals from those cells are transmitted to the brain, which then decides whether or not to eat the plant.

Although insects are plants' biggest threat, our early primate ancestors also looked for ways to make use of roots, leaves and fruits that they found in the tropical forests where they lived. Plants became food or medicine, but they could also cause nausea, vomiting or even death.

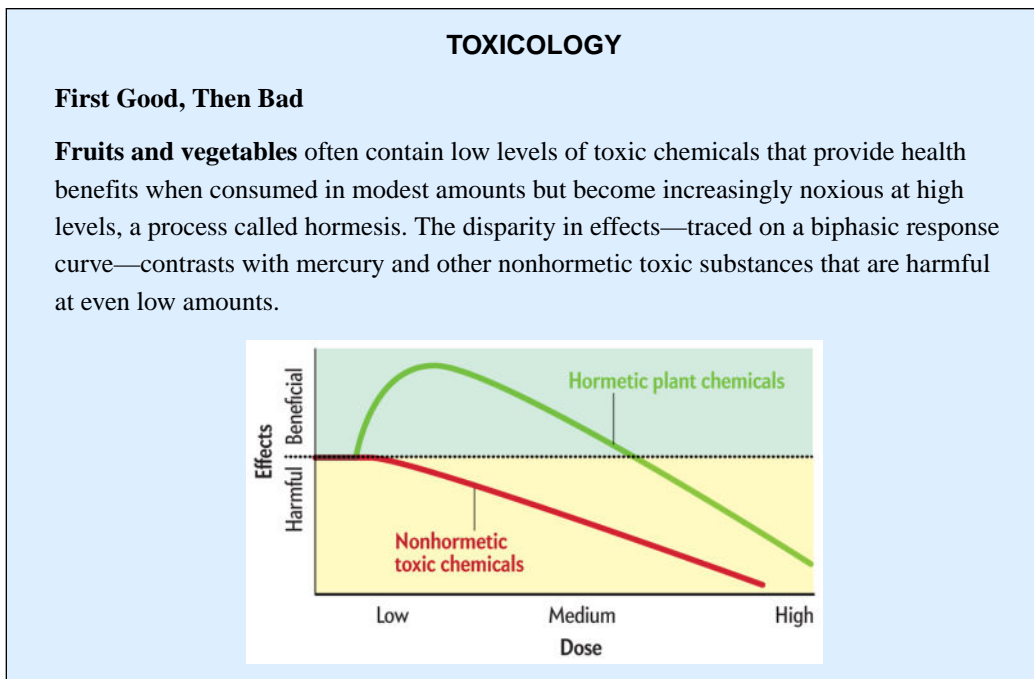
To adapt, we developed an elaborate warning system that reminds me of the behavior of a character in the old television show *Lost in Space*, which was about the adventures of nine-year-old Will Robinson and his family traveling through distant solar systems. When the Robinsons landed on a distant planet and were exploring the terrain surrounding their spaceship, their companion, a sophisticated robot, alerted them of potential dangers. In a 1968 episode called “The Great Vegetable Rebellion,” the robot warned them of the threat of deadly plants.

Much like that robot, our warning system alerts our brain to the presence of toxic substances. The bitter taste of many plants tells us not to eat too much of the bad-tasting leaves, roots and fruits or to simply avoid them entirely. There seems to be some innate justification for children not wanting to eat their broccoli after all. For insects, the noxious chemicals help to drive them off, but for us they serve as a warning to limit our intake.

Traditional healers learned through trial and sometimes fatal error that these same plants had important medicinal uses. Pharmacologists, toxicologists and biochemists are now confirming that plant chemicals that are toxic when consumed at high levels can be hormetic—that is, they provide health benefits when eaten in smaller amounts.

When the effects of hormesis-inducing substances are measured, they yield what scientists call a biphasic response curve. It can be illustrated on a graph plotting effects relative to dose and by drawing a line that traces an upside-down U shape. The effect line rises at first to indicate that eating a small or moderate amount of a plant chemical has beneficial health effects. It then drops gradually to illustrate the toxicity that emerges as more of these substances are consumed. Eating too many Brazil nuts can poison the liver and lungs because of the presence of the trace element selenium. Yet eating just a few supplies an essential nutrient that is incorporated into an enzyme that may help protect against heart

disease and cancer. This example illustrates how hormesis works and differentiates it from homeopathy, which claims, without valid evidence or a plausible mechanism, that vanishingly small amounts of what causes illness can be curative.



Chemicals that induce the just enough/not too much responses characteristic of hormesis seem to be ubiquitous in the plant world. Edward J. Calabrese, a professor of toxicology at the University of Massachusetts Amherst, has spent a large part of his career identifying chemicals that are responsible for hormesis. He has conducted a laborious, three-decades-long analysis of more than 10,000 published studies in the fields of biology, toxicology and medicine. On this list are caffeine, opioids and other compounds that have effects in the brain. Calabrese established a scientific society and a journal devoted to research on hormesis. Because of our common interest in how cells and organisms have evolved to respond to many types of stress and why this is important for human health, he and I co-edited a book on the subject.

Some scientists are now reassessing earlier experiments that seemed to point to a beneficial role for fruit and vegetable antioxidants in the brain—and for general health. They are looking to see whether hormesis may have been responsible for positive results reported in their studies instead. That research and other work appear to confirm that cellular stress induced by plant chemicals may complement or, in some cases, eclipse the contribution of antioxidants. It is not that antioxidants have completely faded from the picture. Rather the biochemical processes set in motion by hormetic stress seem to control when antioxidants are available to be used by brain cells.

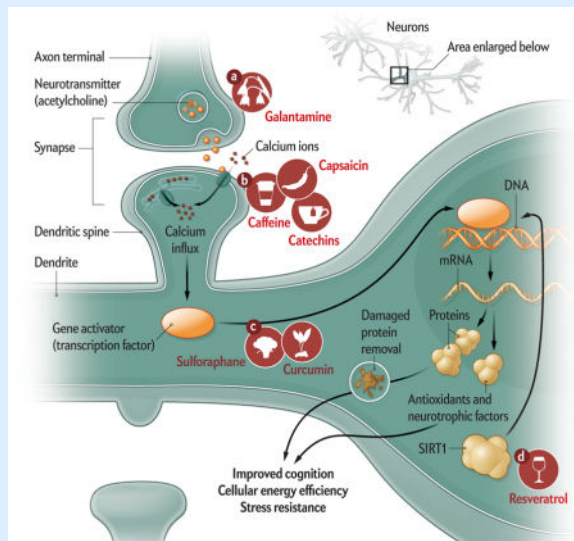
One example of the new line of research comes from Gregory M. Cole, a neuroscientist at the University of California, Los Angeles, who more than a decade ago used an ingredient in curries, curcumin, to perform an experiment that he thought might lead to a treatment for

Alzheimer's. When mice genetically engineered to develop the pathological signs of Alzheimer's consumed curcumin, they experienced less damage to brain cells from free radicals and a diminished buildup of beta-amyloid. At first, Cole thought curcumin worked by removing free radicals. Later experiments in my lab and by others showed, however, that curcumin actually causes a mild stress in brain cells. Stress triggers the production of antioxidant enzymes that tamp down both free radicals and the accumulation of toxic proteins. The health benefits of curcumin on the brain appear to be wide-ranging. Other animal studies with curcumin suggest that it may reduce damage from stroke and may even help alleviate depression and anxiety.

## HOW PLANT CHEMICALS HELP

### Building Brain Resilience

**Investigators have traced** the ways that various hormetic chemicals in plants act on signaling pathways to enhance the functioning of neurons. Galantamine, extracted from snowdrops, increases levels of acetylcholine (*a*), which is deficient in Alzheimer's disease. Once released from the tip of one neuron, acetylcholine stimulates another neuron by binding to a receptive site known as a dendritic spine. Caffeine, capsaicin from hot peppers and catechins from tea (*b*) act on channels in the cell membrane to allow entry of calcium ions that turn on the cell's protein-making machinery (DNA and RNA). Inside the cell, sulforaphane from broccoli, curcumin from turmeric (*c*) and resveratrol from grapes (*d*) also trigger activity of genes or a gene-regulating protein (SIRT1). These chains of biochemical events produce antioxidants or neurotrophic factors and eliminate damaged proteins—all of which bolster stress resistance, regulate cellular energy efficiency and, most important, improve overall cognition.



Still more ingredients in curry may be good for the three-pound organ inside our skull. Garlic and hot peppers both contain chemicals that open a channel in the outer membrane of neurons to let calcium ions enter. The opening of these channels causes higher than normal levels of electrical activity in neurons, a stress that in animal models seems to protect the

cells from the hyperactivity that occurs during a stroke. People living in countries where garlic or hot peppers are widely consumed tend to maintain excellent brain function as they age, although it still remains to be seen whether these plant chemicals or other aspects of their diet and way of life are responsible.

Hormesis seems to be at work in all these studies—and this insight creates an increasingly complex picture of the interaction of free radicals with antioxidants. Curcumin does not function to directly neutralize free radicals. Instead it calls in enzymes and other reserve troops that protect against these molecules. This carefully synchronized process may explain why antioxidant supplements often prove ineffective or even harmful.

Dousing the body with supplements may inhibit the natural stress response throughout the body. In one 2009 study researchers at Friedrich Schiller University Jena in Germany and their colleagues showed that after a month of exercising and taking antioxidant supplements, a group of men had no improvement in regulation of blood glucose and other health indicators, whereas men who only exercised did benefit. The implication is that antioxidant supplements may actually negate the health effects of exercise by impeding hormesis.

The biochemical pathways that bolster the body's resistance to plant chemicals are becoming clearer. One of them involves two proteins, called Nrf2 and Keap1, that are normally bound together in the cytoplasm, the area outside the cell nucleus. When exposed to plant chemicals such as curcumin or the sulforaphane in broccoli, Keap1 releases Nrf2, which then moves into the cell nucleus. There it activates genes that encode antioxidant enzymes that eliminate free radicals. Sulforaphane stimulates the Nrf2 pathway to rid the body of an overabundance of free radicals. In a petri dish, it can protect cells in the eye from the ultraviolet light damage that causes macular degeneration.

This connection between plant chemicals and the Nrf2 pathway has also motivated my own work. About seven years ago I happened across a book entitled *Insect Antifeedants*, by Opendar Koul, an Indian scientist and expert on natural pesticides produced by plants. Koul catalogued more than 800 chemicals that have been isolated from plants and shown to prevent insects from feeding on them. My lab obtained about 50 such insect antifeedant chemicals and tested their ability to activate one or more stress adaptation signaling pathways in cultured neural cells. Several of the chemicals activated the Nrf2 pathway and exhibited the classic biphasic response curve characteristic of hormesis. Particularly effective was a chemical called plumbagin, which is present in a type of tropical flowering plant and in black walnuts. We found that plumbagin was very effective in reducing brain damage and improving the prognosis for recovery in mice that model stroke. The next step we and others are contemplating is to test neuroprotective chemicals such as sulforaphane and plumbagin in human patients.

Another key cellular defense involves a family of proteins called sirtuins. Leonard Guarente of the Massachusetts Institute of Technology found that one of the sirtuins, SIRT1, can increase the life span of yeast cells and plays a key role in the extension of life span by caloric restriction. Resveratrol, found in red grapes and wine, appears to activate SIRT1, which then switches on multiple chemical pathways that mediate hormetic effects. In animal



studies, resveratrol guarded the brain and spinal cord against damaging effects from the cutting off of blood flow that occurs in some types of stroke. Not all of the research is uniformly positive. Scientists still need to determine whether one of the pathways activated by resveratrol may actually speed the death of some neurons.

These studies have been complemented by other research showing that timing of the stress response in a cell is critical to whether the cell benefits from it. Just as vigorous exercise—another source of hormetic effects—needs to be interspersed with periods of rest for growth and repair of cells, so apparently does consumption of plant chemicals. When consuming fruits and vegetables, the body enters a so-called stress-resistance mode, characterized by an overall reduction in the making of new proteins, an increase in the removal of damaged molecules and the production of proteins specifically needed for cell survival.

Cells can endure in this state for only so long before they need to make new proteins for other purposes, become overstressed and begin to deteriorate. When the stress is removed, protein synthesis increases, and the cells grow and repair molecular damage that may have occurred. In the case of neurons, new connections among cells can form during the recovery period. Findings suggest consumption of fruits and vegetables or adopting an exercise regimen—followed by a period of rest—can stimulate the production of new neurons from stem cells located in a structure deep within the brain called the hippocampus. The new neurons then grow and form connections with existing neurons, effectively increasing learning and memory capacity. In practice, a normal period of sleep at night may be sufficient for cells to recover from exercise or exposure to plant chemicals consumed during the day.

## DRUG LEAD FROM UWHANGCHUNGSIWON

Hormesis may open the way to look for new drugs—and may explain the mechanism of some already approved drugs. Snowflake and snowdrop flowers produce galantamine, a chemical that can improve memory by increasing levels of acetylcholine, a brain-signaling molecule in synapses, the connecting points between neurons. Galantamine, now a prescribed drug that has a modest beneficial effect on Alzheimer's symptoms, creates a mild stress in neurons that appears to protect them against neurodegeneration while improving their ability to use chemical and electrical signals to communicate with other neurons.

New leads for hormetic drugs may come from delving into the lore of herbal medicine. A substance known as uwhangchungsimwon, used in the traditional Korean pharmacopoeia to treat stroke, may protect neurons by inducing a stress response that results in the making of proteins, such as Bcl-xl, that prevent cells from dying. Chemicals from hallucinogenic plants may offer leads as well; when administered in moderate doses in a controlled clinical setting, they have shown promise for treating anxiety, depression and drug addiction.

The concept of hormesis has not escaped its share of controversy. Some researchers question whether scientists have developed adequate methods for distinguishing when a beneficial effect ends and a toxic one begins. The exact threshold for when a toxic reaction starts may vary by individual, making it difficult to use hormesis as a basis for drug therapies.

Skepticism arises, too, when the basic concept is extended to ionizing radiation, such as x-rays, for which low doses have been shown to have beneficial effects on healthy lab animals. Various scientific advisory bodies, however, have rejected radiation as unsafe for humans even at the lowest levels.

Evaluating the potential health benefits of hormesis will require careful randomized clinical trials because many herbs are marketed with unsubstantiated claims about their efficacy. The National Center for Complementary and Integrative Health was established in 1998 in part to help fund studies of such compounds.

These challenges should not preclude continuing research on hormesis. Plant chemicals that induce a cellular stress may have advantages over traditional pharmaceuticals, which cause side effects by disrupting the normal functioning of nerve cells. Diazepam (Valium) acts on brain cells in ways that reduce anxiety but also cause drowsiness. The drug switches off a neural circuit, and that circuit stays off until the effects of the drug wear off. At the proper dose, drugs that rely on hormesis would not adversely affect circuit activity and so would be expected to have fewer side effects.

Some labs, including my own, are pursuing development of hormetic drugs and have generated encouraging results in animals genetically engineered to mimic several neurodegenerative diseases in humans. Early research shows that these drugs protect nerve cells from dying and that the cells become better able to resist an onslaught of free radicals and molecular damage that wreak havoc in the brain. Perhaps apple skins, walnuts and curry powder will become the raw materials for a radically new generation of treatments for brain disease.

## Biography



**Mark P. Mattson** is chief of the Laboratory of Neurosciences at the National Institute on Aging and a professor of neuroscience at the Johns Hopkins University School of Medicine. His discoveries have advanced understanding of nerve cell circuits during aging.



**IN BRIEF**

**Plants** do not have the option of fleeing predators. As a consequence, they have developed an elaborate set of chemical defenses to ward off insects and other creatures that want to make them into a meal.

**Toxic chemicals** that plants use against predators are consumed by us at low levels in fruits and vegetables. Exposure to these substances causes a mild stress reaction that lends resilience to cells in our bodies.

**Adaptation** to these stresses, a process called hormesis, accounts for a number of health benefits, including protection against brain disorders, we receive from eating broccoli and blueberries.