

Lithium to the Rescue

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Editor's Note: Lithium, an element that Mother Nature has put in some drinking water sources, has been used for its curative powers for centuries. Today, it's given in capsule form as a mood stabilizer for bipolar disorder and depression. New research, however, reveals its role as a neuroprotector, and suggests that a better understanding of the role enzymes modulated by lithium play could lead to new treatments for Alzheimer's disease, Parkinson's disease, multiple sclerosis, and other neurodegenerative disorders.

In the popular television series *Homeland*, lithium is among the medications used by the bipolar disorder-afflicted main character, Carrie, played by Claire Danes. When Carrie is off her meds, her judgment is compromised, and chaotic situations tend to worsen. At one point last season, Carrie went off her lithium because she mistakenly believed it would help her improve her concentration.

Although most people are better acquainted with lithium through shows such as *Homeland* and other forms of popular culture, others know of it because of its use in a clinical setting. Individuals typically take lithium for bipolar disorder, a condition that involves cycles of mania and depression and is often referred to by its previous name—manic-depressive illness.

TV stereotypes aside, growing evidence suggests that low levels of lithium may strengthen the brain's resilience to stress and disease. There is now a substantial understanding of how lithium can strengthen and protect the brain.

Few people realize that lithium is the simplest molecule in any pharmacopoeia. Lithium is simply a small, positively charged element, similar to sodium. In nature (found in groundwater, for example) and in medicine charged molecules are neutralized with a counterbalancing molecule. As a result, lithium is attached to a negatively charged molecule, such as chloride, to form the uncharged compound lithium chloride.

A Long History

Lithium was used inadvertently in medicine long before it was identified as a unique element in the early 1800s. It was used for maladies of many kinds, from centuries of “taking the waters” at Marienbad, Vichy or Baden Baden, and other sources of “healthy waters,” which often were naturally enriched in lithium, to the more recent popularity of ingesting “lithium-fortified” beverages for improving health and immunity in the 20th century. The popular soda, 7-Up, was supplemented with lithium until 1950, for example.

In the 1950s, when clinical trials of lithium were first conducted, it became clear that lithium had the capacity to stabilize mood in about half of the patients with bipolar disorder. Indeed, lithium

remains the “gold standard” of treatment for bipolar disorder to which all subsequent treatments are compared. It is generally considered the most effective mood stabilizer for the severe disorder’s manic and depressive components. Lithium’s clinical efficacy set in motion the current research effort to better understand lithium’s mechanisms of action. Its untapped potential may well be considerable and beneficial in the treatment of several other diseases.

Brain Protector

Understanding the causes of diseases and how therapeutic drugs work is a long, arduous process. Research into how lithium stabilizes mood in bipolar disorder patients has been no exception. Many different effects of lithium were found by researchers studying different kinds of cell types, organs, and organisms. However, the difficulty lay in determining which of these actions was important for its therapeutic effect.

In 2002, Drs. Hussein Manji and Carlos Zarate¹ organized a wonderful little conference to which they invited leading mood disorder researchers to present their best ideas about how mood stabilizers such as lithium work. Not surprisingly, a large number of different possibilities were presented. Our own contribution was to present evidence that an important action of lithium was its neuroprotective effect. Recognized for several years, this action was mediated by its inhibition of an enzyme called glycogen synthase kinase-3 (GSK3).² The idea was based on the discovery by others that lithium inhibits the activity of GSK3,³ and the discoveries that GSK3 inhibition protects neurons from a wide variety of insults, including oxidative stress, impaired mitochondrial functions, DNA damage and excitotoxicity.^{4,5} GSK3 is an enzyme in a class known as a kinases that transfer phosphate groups to other proteins to regulate their activities.

Not surprisingly, most of our colleagues were skeptical and followed other directions in their research. This skepticism was partially based on the fact that the neuroprotection offered by lithium and other inhibitors of GSK3 was first detected in experiments measuring the death of neurons, whereas psychiatrists widely believe that neurons in patients with bipolar disorder do not die. Unappreciated by many at the time was the concept that neurons undergo a number of degenerative changes that impair their functions long before they actually die. Examples of impairments that often occur well before cell death are weakening or loss of connections

(synapses) between neurons that are required for communication, pruning of cell processes such as dendrites and nerve terminals, changes in the function of the mitochondria that produce the energy used by cells, stress responses in cells (such as in the endoplasmic reticulum stress), loss of the protective myelin sheaths around neuronal axons, and DNA damage.

Over time, it became evident—and has become accepted in the past decade—that although lithium can sometimes stave off neuronal death, probably most of its clinical benefit comes from its prevention of these impairments that precede neuronal death. It is also important to note that lithium is not only neuroprotective but is also one of the psychopharmacological agents that increases new neuron production (neurogenesis) in the hippocampus, a critical brain area for learning, memory, and stress responses.⁵

Many people wonder how a small element such as lithium can be neuroprotective and interact with only a very small number of proteins such as GSK3. Recent studies of the structures of proteins reveal that a few contain a small pocket in which lithium fits perfectly.⁶ When lithium is in the pocket, it acts like a stone in a cog, blocking the normal workings of the protein. GSK3 is such a protein. When lithium is in the pocket of GSK3, it blocks the actions of GSK3 and consequently alters the actions of numerous proteins that are regulated by GSK3.

One of the effects of GSK3's phosphorylation activities is to facilitate signals that cause neurons to die.⁴ This is a normal process during development when the brain needs to rid itself of excessive neurons. Unfortunately, in many neurodegenerative conditions, including Alzheimer's disease, Parkinson's disease, traumatic brain injury, and ischemia following stroke, the mechanisms causing neuronal death are abnormally activated. The large number of people afflicted with these conditions makes it critical to better understand lithium's neuroprotective effects to determine if it may be beneficial in such cases.

Biochemical Mechanisms

That lithium can produce many effects in cells was somewhat surprising for a while, given the small number of proteins with which lithium directly interacts. However, lithium's unusual breadth of activity appears to result from its inhibition of GSK3, which itself regulates the functions of more

target proteins than any other kinase through the phosphorylation mechanism noted above.⁷ In fact, GSK3 is known to phosphorylate, and thereby regulate, more than 100 proteins. A good number of these play roles in regulating neuronal resilience to stress.

GSK3 is activated when neurons are stressed by any of a large variety of mechanisms, such as oxidative stress, endoplasmic reticulum stress, DNA damage, and exposure to toxic chemicals or proteins.⁷ Activated GSK3 then has an increased influence on cellular proteins and functions, often promoting the deleterious effects of stress on neuronal functions that in severe conditions can cause neuronal death. Lithium can bolster the resilience of neurons by inhibiting GSK3 to put a brake on the deleterious effects of stress and toxic substances.

One large class of proteins regulated by GSK3, and hence by lithium, are transcription factors.⁷ Transcription factors regulate the expression (i.e., transcription) of genes, thereby regulating the levels of proteins that are present in cells. GSK3 is now known to regulate the actions of more than 25 different transcription factors, thereby exerting a tremendously large effect on regulating the levels of proteins in neurons. For example, GSK3 inhibits the transcription factor called CREB--which otherwise contributes to cellular resilience and learning and memory, in part by inhibiting the expression of the signaling protein BDNF. Lithium effectively frees CREB to do its beneficial work. Lithium also increases resistance to oxidative stress by reversing GSK3's inhibition of the transcription factor Nrf2. Moreover, lithium counters GSK3's activation of the transcription factor p53, which promotes cell death in response to certain stresses. Thus, lithium's inhibition of GSK3 can bolster the actions of CREB and Nrf2, and diminish the action of p53, to promote neuronal resilience.

Lithium's inhibition of GSK3 also contributes to an array of other neuroprotective actions too numerous to discuss. Well-documented outcomes include axonal regeneration, improved mitochondrial function, re-myelination, and the generation of new neurons in adult mammalian hippocampus (neurogenesis). These neuroprotectant and neurorestorative actions of lithium each depend on modifications of different proteins in each process, often mediated by GSK3. Thus, lithium has the capacity to provide neuroprotection in many conditions that exert distinct deleterious effects on neurons.

Lithium's Vast Potential

While lithium is well-established as an effective therapy for many patients with bipolar disorder, recent research in rodent models has found evidence that it also may provide clinically significant neuroprotection in other conditions.

As mentioned above, a number of toxic proteins and chemicals that adversely affect, or stress, neurons are capable of activating GSK3 in neurons, and several of these have been linked to diseases. For example, Alzheimer's disease appears to be caused in part by abnormal accumulation of a protein called A β , which is the primary component of amyloid plaques that develop in the brains of patients with Alzheimer's disease. A β has been shown to activate GSK3, which in turn causes abnormal phosphorylation of a protein called tau, the primary component of neurofibrillary tangles in Alzheimer's disease brains.⁸ Thus, GSK3 is intimately involved in the neuropathological hallmarks of Alzheimer's disease, as well as in the death of neurons.

An exciting possibility is that lithium may delay the devastating pathology and neuronal loss that occurs in Alzheimer's disease. This possibility is supported by evidence that dementia is less prevalent in patients with bipolar disorder that have been taking lithium for long periods of time, though this is only a correlative association.⁹ The strong theoretical basis for lithium therapy led to some early trials of lithium in patients with Alzheimer's disease, which revealed mild beneficial effects of lithium.^{10,11} However, the effects of lithium may be improved by initiating treatments very early in the disease, before neurons are damaged beyond repair. In determining therapeutic effectiveness, it's also likely that lithium and other treatments need to be given for several years to test the beneficial effects in a clinical trial—although a long trial is a very difficult task.

The apparently abnormal activation of GSK3 in neurons is seen also in Parkinson's disease,¹ stroke, and traumatic brain injury. Using lithium to inhibit GSK3 may therefore have some benefit in these disorders as indicated by its protective effects in animal models of these conditions.¹²⁻¹⁴

Another important neuroprotective mechanism of lithium's inhibition of GSK3 appears to be the control of inflammation.¹⁵ Inflammation is associated with systemic disorders, such as rheumatoid

arthritis and Crohn's disease, and is also evident in many brain diseases, including Alzheimer's disease, Parkinson's disease, and stroke. It is also particularly important in multiple sclerosis.

Injury and infections are known to activate inflammation, but less well-known is the fact that stress can activate inflammation. Inflammation is a double-edged sword. In some conditions it is essential for surviving pathogenic infections. However, uncontrolled or aberrant inflammation, which may occur in response to stress, can be detrimental to neuronal functions. Lithium is a surprisingly effective controller of inflammation, at least in part by its inhibition of GSK3. In animal models and studies in cells, lithium and other GSK3 inhibitors strongly reduce inflammation.¹⁶ This anti-inflammatory effect of inhibiting GSK3 was sufficient to induce remission of the clinical symptoms in animal models of multiple sclerosis.¹⁷ Thus, the anti-inflammatory actions of lithium likely make an important contribution to its neuroprotective capacity.

Lithium may also be effective in treating Fragile X syndrome (FXS), for which no effective therapy exists. FXS is caused by inherited gene mutations that result in intellectual disability and other behavioral disturbances. GSK3 is abnormally active in the brain of animal models of FXS.¹⁸ Inhibition of GSK3 with lithium or other drugs effectively reverses many of the abnormal characteristics in the mouse model of FXS, including reversing impairments in some forms of learning and memory. Intriguingly, lithium is the only treatment as yet found to improve cognition in patients with FXS.¹⁹ The neuroprotective mechanisms of lithium in FXS remain to be identified, but are thought to involve improving synaptic communication between neurons.

Finally, a particularly intriguing finding is that lithium in therapeutic doses in bipolar patients significantly reduces suicide rates. Even small amounts of lithium may effectively diminish suicidal behavior.^{20,21} Several epidemiological studies found that locales with higher natural levels of lithium in the drinking water have lower suicide rates than those with less lithium.²² Although only correlative, these data are consistent with studies in patients that demonstrate that therapeutic levels of lithium reduce suicidal behavior in bipolar patients. How lithium alters neurons to diminish suicide is currently under intense investigation, as there are few other interventions available that reduce suicide, most notably the atypical antipsychotic clozapine.

We should also note that there is also currently much interest in the ability of very low doses of lithium to work synergistically with other therapeutic drugs. For example, Chuang and colleagues pioneered the notion that low doses of lithium synergistically cooperate with low doses of another mood stabilizer, valproate, or the investigational antidepressant ketamine.²³ Investigators have reported particularly strong damage-preventing effects of combined low doses of lithium and valproate in mouse brains after experimental stroke.

Possible Limitations

New is fashionable in clothes, cars, and even drugs—people frequently crave the latest thing. Yet when the need arises, we often rely on the wisdom of our ancestors for guidance. Folk medicine has touted the benefits of lithium for many years, and scientific research is now providing answers to how lithium protects the brain from a wide range of conditions, and for which diseases lithium therapy may be most effective.

While our story has focused on neuroprotective effects of lithium that derive from its inhibition of GSK3, this focus is not meant to overlook the possibility that other targets of lithium may also contribute to its neuroprotection. It is also important to note that lithium treatment is not without limitations, as side effects can limit its utility; doses must be carefully monitored because high therapeutic levels can be toxic.

It is also important to emphasize that, except for bipolar disorder, lithium is likely to be most effective when used in conjunction with other therapies that are aimed at targets specific to each disease, such as the mechanisms that generate toxic proteins and chemicals. Although lithium provides neuroprotection, the effects of many insults are too powerful to be overcome by any individual known treatment. As a result, therapies aimed at reducing the toxic insults combined with lithium's neuroprotective abilities may prove to be most useful to ameliorate conditions involving loss of neuronal functions.

Bios

Richard S. Jope, Ph.D., is a professor in the Department of Psychiatry and Behavioral Sciences and in the Department of Biochemistry and Molecular Biology at the University of Miami School of Medicine. He obtained a Ph.D. in biological chemistry at UCLA in 1975, followed by postdoctoral training in pharmacology at UCLA. During his postdoctoral fellowship he began to study the mechanism of action of lithium, publishing his first research paper on lithium in 1978 in the *New England Journal of Medicine*, which has been followed by over 100 papers and book chapters focused on lithium's actions. Upon moving to a faculty position at the University of Alabama at Birmingham School of Medicine, he obtained funding from the NIH to study lithium in 1984, a project that continues to be funded to identify the therapeutic actions of lithium.

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