A New Element on the Supplement Scene

Can Lithium Benefit Brain Health?

New research shows this element to have a variety of *neuroprotective* properties

By Will Block

Remember when people thought that mental illnesses, such as schizophrenia or chronic depression, were "all in the mind"? You do? Then you may be "youth-challenged," because it's been many years since that quaint old idea bit the dust. We've known for a long time that mental disorders are the result of physical and chemical disturbances in the brain—but deducing the molecular mechanisms involved is a tremendous challenge for neuroscientists. Some diseases are at least partially understood at that level, but many others remain mysterious.

The human brain is the most complex object in the known universe, so it's perhaps forgivable that we haven't figured it all out yet. Not to mention the ultimate paradox: the only thing we have with which to understand the workings of our brains is . . . our brains. (That one gives some philosophers nightmares.)

Meanwhile, neuroscientists keep trying to unravel the mysteries of the brain, bit by bit, while clinicians keep looking for newer and better ways to treat mental disorders—whether the neuroscientists can explain the rationales for them or not. Often the time lapse between discovering that something works and understanding *why* it works is very long indeed. One example is the use of **lithium** for treating bipolar disorder, also called manic-depressive illness or just manic depression. This is the disease in which, for no apparent reason, the patient's mood and behavior alternate between the extremes of mania (a kind of exaggerated and unfounded elation) and depression, usually in cycles of months or years.

Lithium Works—But How?

We've known for half a century that lithium can control the mood extremes of bipolar disorder, and lithium-based drugs have been successfully used as therapy during that time. Lithium's mechanism of action on the brain is still unknown, however. It has been speculated—and there is some evidence for this—that it may affect the levels of the neurotransmitters serotonin and norepinephrine in the brain. There is also evidence that lithium inhibits the action of inositol monophosphatase and several other enzymes that play key roles in mood-related neuromodulation (a complex type of signaling process related to neurotransmission).

And now there is growing evidence that lithium may provide some degree of protection against the brain damage that is characteristic of neurodegenerative diseases, such as Alzheimer's. Before we discuss this exciting new avenue in dementia research, however, let's talk a bit more about the use of lithium in treating bipolar disorder.

Lithium Is Still the Treatment of Choice

Long before anyone knew about lithium, let alone neurotransmitters or enzymes, it had been noticed that the waters of certain mineral springs seemed to have curative powers for people suffering from mania or depression. In the second century A.D., the Greek physician Seranus Ephesios recommended "natural waters such as alkaline springs" as a treatment for mania. Over the ensuing

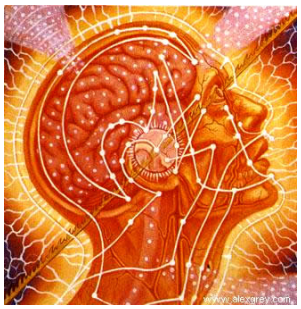
two millennia, countless people have “taken the waters” for a variety of ailments, real and imagined, at fashionable (and not so fashionable) spas throughout the world, particularly in Europe.

We now have an idea why these waters often seemed to helped manic individuals calm down, or depressed individuals perk up: it may have been not just the soothing spa ambience, but perhaps also the lithium in the water, which the spa clients were encouraged to drink as well as to soak in.

Lithium is so effective in controlling the mood extremes of bipolar disorder that to this day it is still the treatment of choice, even though a variety of effective, but sometimes dangerous, synthetic drugs have also come on the scene. The fact that lithium controls both mania *and* depression (the former more effectively than the latter) is both wonderful and puzzling, as it suggests that both of these conditions are, somehow, symptoms of the same underlying neurochemical disturbance.

It’s sobering to realize, though, that bipolar disorder goes beyond mere molecular imbalances: it also entails measurable losses of brain matter owing to neuronal death in a number of regions of the brain, including the hippocampus, a region that is also particularly hard hit by neuronal loss in Alzheimer’s disease.

Lithium Therapy Requires Careful Management



A typical maintenance dosage at which lithium (usually in the form of lithium carbonate) is prescribed for controlling bipolar disorder is 900 milligrams of the carbonate per day, which is equivalent to 170 mg of elemental lithium.* **This is about 100 times greater than the amount of lithium (3.5 mg) contained in 1 liter of water from the famous Lithia Mineral Springs mineral springs in Georgia**, and it’s hundreds of times greater than the trace amounts that we normally ingest with our food (about 200–600 micrograms per day). Thus, by either Lithia Mineral Water standards or nutritional standards, the therapeutic dosages of lithium are very high. That would be all right but for one thing: these therapeutic dosages are perilously close to being *toxic* dosages—not a good situation for any kind of medicine. For every patient, therefore, the physician must individualize and carefully monitor the treatment to avoid toxic overdosage.

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*The lithium is in the form of lithium ions, of course. The maintenance dosage produces plasma lithium-ion concentrations of about 0.6 millimoles per liter, which represents the low end of the desired “therapeutic range” of about 0.6–1.5 millimoles per liter (4–10 milligrams per liter). For laboratory studies with cell cultures, researchers generally use lithium solutions within this range of concentrations so as to mimic real-life clinical conditions, and for animal studies they use dosages that will produce plasma lithium-ion concentrations in this same range.

At these high levels, there are also many potential side effects of lithium, ranging from minor to severe. Among the most common (and benign) are dizziness, drowsiness, diarrhea, nausea, vomiting, excessive urination and thirst, a metallic taste, shakiness, tremors, and weight gain.

Lithium Inhibits Plaques and Tangles

Lithium solutions (usually lithium chloride or lithium carbonate same as the Lithium found in Lithia Springs Mineral Water) in the therapeutic range or beyond have been used in several recent laboratory and animal studies, and one human study, that have intriguing implications for preventing or inhibiting the progression of Alzheimer's disease.

One such study dealt with the relationship between two of the three most characteristic neuroanatomical features of Alzheimer's: the formation in the brain of harmful proteinaceous deposits called *amyloid-beta plaques* and *neurofibrillary tangles.*[1] Both of these contribute to the death of brain neurons—which is the third characteristic feature. It turns out that the plaques are partly responsible for the formation of the tangles, and the researchers discovered that lithium (at about 10 times the therapeutic dosage) blocked this process in cultured rat cortical neurons, resulting in a strong protective action against neuronal death. In effect, the lithium protected against the neurotoxicity of amyloid-beta (which is also called beta-amyloid).

In a related study, researchers used mouse cortical neurons and live mice that were bred to be highly susceptible to Alzheimer's disease.[2] They found that treatment with lithium in therapeutic doses (for 3 weeks in the case of the live mice) sharply reduced the production of amyloid-beta in the first place, apparently by inhibiting the action of an enzyme, glycogen synthase kinase-3-alpha (GSK-3-alpha), that is required for this process to occur, as well as for the production of neurofibrillary tangles. The reductions observed were in the range of 40–78%. [Certain nonsteroidal anti-inflammatory drugs (NSAIDs) also reduce amyloid-beta levels, by the way, and the authors speculated that combination therapy with lithium and an NSAID might have an enhanced effect.*]

Lithium Protects Against Neuronal Death

In a third study, researchers examined the effects of lithium on *glutamate-induced excitotoxicity,* which is neuronal death caused by excessive amounts of glutamate, the brain's most prevalent neurotransmitter.[4] This phenomenon has been strongly implicated in the origin of a variety of neurodegenerative diseases, including dementia. The researchers found that lithium in the therapeutic range largely prevented glutamate-induced excitotoxicity in rodent cortical neurons. It apparently did so by stimulating the production of a protective protein called *brain-derived neurotrophic factor,* or BDNF, which is vital for the development and maintenance of healthy neurons (neurotrophic means pertaining to neural nutrition). Evidence for this mechanism came from the observation that when an antibody that neutralizes BDNF was added to the culture, lithium's neuroprotective effect was blocked.

Lithium Stimulates New Neuronal Growth

Protecting neurons from destruction is one thing; it's quite another to stimulate the growth of new neurons—a process called *neurogenesis.** Numerous factors can affect neurogenesis, and lithium is apparently one of them. Researchers treated mice with lithium in dosages that produced plasma concentrations equivalent to those in the human therapeutic range; then they killed the mice and examined their brains.[5] They found a 25% increase in the number of dividing cells in a structure of the hippocampus called the dentate gyrus—a clear indication of neurogenesis. This fit with the fact that lithium is known to stimulate production of a brain protein called B-cell lymphoma protein-2 (bcl-2) in certain areas of rodent brains; bcl-2 not only actively protects neurons from a variety of threats, including apoptosis (programmed cell suicide), but also promotes new cell growth.

(Hippocampal neurogenesis has also been observed with a variety of antidepressants, so lithium's action in this regard is not unique.)

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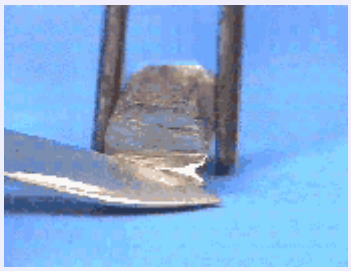
*Until the late 1990s, it was widely believed that neurogenesis could not occur in adult human brains. We now know, however, that it can occur, and does.

A Lithium Primer



Lithium is an odd element that most people don't know much about. Like the more familiar elements sodium and potassium, lithium is an alkali metal, and its chemical properties derive from that fact. It's the lightest of all metals, with a density only half that of water. Thus it floats in water, with which it reacts chemically, producing hydrogen gas. It also reacts rapidly with oxygen, and it's the only element that reacts with nitrogen at room temperature. With such extreme chemical reactivity, it obviously can't be stored in air or water, so it's usually stored in kerosene, with which it does *not* react. Lithium is so soft that it can be cut with a knife.

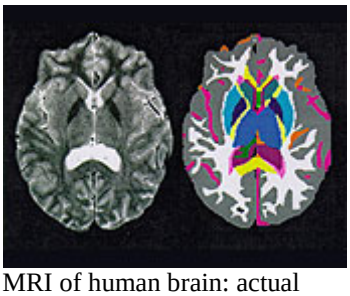
Not surprisingly, lithium (from the Greek *lithos*, meaning stone) is never found in nature as the free metal, but only in the form of stable chemical compounds (from which the free metal can be produced). These compounds are found in small amounts in nearly all igneous rocks (rocks formed by volcanic action), but the primary sources of lithium are the alkaline waters of many mineral springs and certain salt lakes, such as Searles Lake in California.

The main uses of lithium are in batteries, medicines, alloys (it increases corrosion resistance and tensile strength), lubricants, ceramic glazes, nuclear reactors, and hydrogen bombs.

Lithium compounds are found in trace amounts in fish, processed meat, dairy products, eggs, potatoes, and vegetables; we ingest only about 200–600 micrograms of lithium daily. Although lithium is not one of the nine trace elements that are vital for human nutrition (because without them, life itself would not be possible), it is one of the 14 (and perhaps more) auxiliary trace elements that are believed—with widely varying degrees of evidence—to be essential for our health.

Lithia Mineral Water is an excellent natural source of Lithium in trace amounts that has tremendous benefits to your mental and physical well being. The health benefits of Lithium are greatly misunderstood, because it is not just for bio-polar people and people with mental disorders. In fact, lithium is essential for overall mental and physical health for normal everyday active people. If your body is deficient in Lithium then you will experience mood swings, depression and other type of mild to serious mental disorders. In fact, the human body cannot survive without Lithium. Lithia Mineral Water is an excellent all natural source of trace amounts of essential Lithium that is a perfect way to start the day for mental and physical well being.

Lithium Increases Gray Matter



MRI of human brain: actual (left) and artificially colored (right) to illustrate different neuroanatomical features.

Finally, researchers at the Wayne State University School of Medicine in Detroit studied ten human patients (average age 33) with bipolar disorder.[6] For 4 weeks they gave the patients a daily therapeutic dosage of lithium (they didn't specify the actual dosage, but rather the plasma lithium-ion concentration that resulted from it—about 0.8 millimoles per liter, which would have required roughly 1000 mg per day of lithium carbonate). They then did magnetic resonance imaging (MRI) of the patients' brain and compared the scans with those taken at the outset of the study. In eight of the ten patients' brains, the lithium treatment significantly increased the total volume of gray matter: the average increase was 3%, corresponding to a volume of about 24 cm^3 (1.5 $in.^3$). The authors attributed the effect to lithium's neurotrophic properties and its ability to stimulate the growth of such non-neuronal objects as glial cells, but they did not describe it as neurogenesis.

Lithium Might Be Helpful in Alzheimer's

In all five of the studies outlined above, the researchers concluded their reports with statements to the effect that their results, along with those of various other recent studies, point to the possibility that long-term treatment with lithium might prove useful for reducing brain damage and stimulating new neural growth in neurodegenerative diseases such as Alzheimer's.

That's encouraging, and it illustrates the value of looking constantly for new (or old) and better ways to attack the problem of Alzheimer's disease and other age-related diseases, so that we can all look forward to longer, healthier, happier lives.

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Brain Chemistry Basics

You've probably heard the term "neurotransmitter" before, but what does this really mean? Neurotransmitters are chemical messengers within the brain that facilitate communication between nerve cells.

Let's illustrate with serotonin. Figure 1 depicts the junction between two nerve cells. Packets of serotonin molecules are released from the end of the presynaptic cell (the axon) into the space between the two nerve cells (the synapse). These molecules may then be taken up by serotonin receptors of the postsynaptic nerve cell (the dendrite) and thus pass along their chemical message. Excess molecules are taken back up by the presynaptic cell and reprocessed.

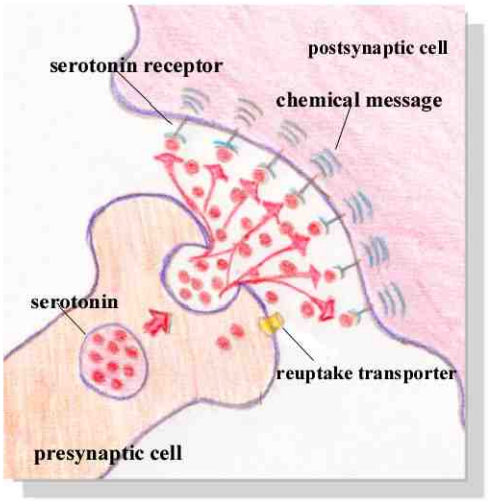

Figure 1
Image by Nancy Schimelpfening

Several things might potentially go wrong with this process and lead to a serotonin deficit. Just to enumerate a few possibilities:

> Not enough serotonin is produced,
> There are not enough receptor sites to receive serotonin,
> Serotonin is being taken back up too quickly before it can reach receptor sites,
> Chemical precursors to serotonin (molecules that serotonin is manufactured from) may be in short supply, or Molecules that facilitate the production of serotonin are in too short supply.

As you can see, if there is a breakdown anywhere along the path, neurotransmitter supplies may not be adequate for your brain's needs. Inadequate supplies lead to the symptoms that we know as depression.

The Primary Players

There are three basic molecules, known chemically as monoamines, which are thought to play a role in mood regulation: **norepinephrine, serotonin, and dopamine**.

Norepinephrine

In the 1960s Joseph J. Schildkraut of Harvard University cast his vote with norepinephrine as the causative factor for depression in the now classic "catecholamine" hypothesis of mood disorders. He proposed that depression stems from a deficiency of norepinephrine in certain brain circuits and that mania arises from an overabundance of this substance. There is indeed a large body of evidence that supports this hypothesis, however, changes in norepinephrine levels do not affect mood in everyone.

Obviously there must be some other factor that interacts with norepinephrine to cause depression. **Serotonin** has been found to be this other factor. Serious investigations into serotonin's role in mood disorders, however, have been going on for almost 30 years, ever since Arthur J. Prange, Jr., of the University of North Carolina at Chapel Hill, Alec Coppen of the Medical Research Council in England and their co-workers put forward the so-called "permissive hypothesis". This view held

that synaptic depletion of serotonin was another cause of depression, one that worked by promoting, or "permitting," a fall in norepinephrine levels.

So, although, norepinephrine still played a major role in depression, serotonin levels could be manipulated to indirectly raise norepinephrine.

Dopamine

A third substance that may play a role in mood is dopamine. Dopamine is associated with the reward, or reinforcement, that we get which causes us to continue participating in an activity. There is some evidence that, at least for a subset of patients, dopamine plays a role in depression. Dopaminergic substances and stimulants have been used as antidepressants when other measures have failed. Some studies have investigated dopaminergic agents as a rapid method of relieving depression (in contrast to medications which may take up to six weeks to exhibit their full effect).

Self-Medicating?

Although agents that work selectively on dopamine have the benefit of fast action, they have also exhibited some properties which have kept them from being as widely used as other antidepressants. Dopamine is a neurotransmitter that is associated with addiction and it's production is stimulated by drugs such as cocaine, opiates and alcohol (which may explain why depressed persons choose to self-medicate with drugs and alcohol. Drug specifically targeted at dopamine, for example amineptine (Survector), present the potential for abuse. For this reason, amineptine is not approved for use in the US or Britain at this time. There is a natural solution.....increase your daily take of Lithium by drinking just 1 bottle of **Lithium Mineral Water** or **CHIgevity** on an empty stomach when you first start your day. In just a few days see for yourself the difference!

STIMULATION OF SEROTONIN SYNTHESIS BY LITHIUM

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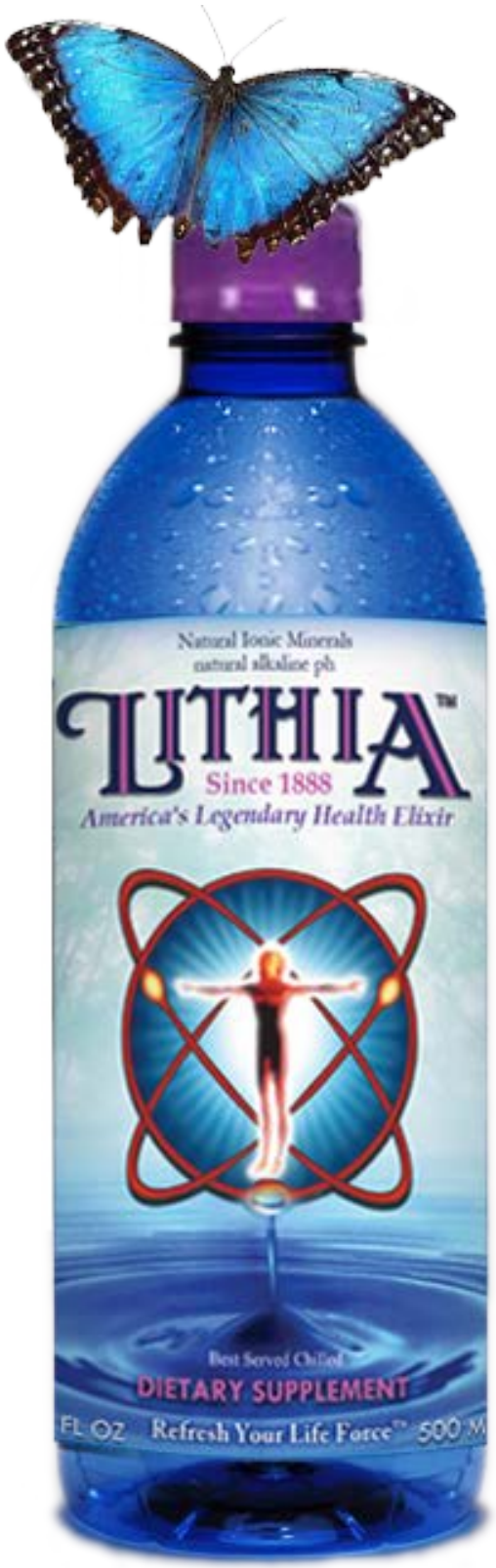
Abstract

Repeated administrations of lithium salts (Li_2CO_3 or LiCl, 60 and 85 mg/kg, respectively, twice a day for five days) to rats increased brain 5-hydroxyindoleacetic acid (5-HIAA) by about 80% and brain serotonin by 15 to 20%. The changes were not due to an inhibition of 5-HIAA transport from brain, but to an increase in the rate of synthesis of brain serotonin. Rate of serotonin synthesis was measured by multiplying the rate constant of 5-HIAA decline, after inhibition of monoamine oxidase, by the steady-state level of 5-HIAA. The calculation indicated that lithium increased the synthesis rate of brain serotonin by about 80%. Moreover, chronic treatment with lithium salts also increased the levels of brain tryptophan by about 70%, suggesting that this could be the mechanism by which lithium stimulates serotonin synthesis. *The full scientific article is available upon request.*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