

Unexpected results from a drug that is also an essential nutrient ...

Lithium is a brain food, with extraordinary properties, even in small amounts

Lithium has long been used as a mood stabilizer in the treatment of manic depression (known today as bipolar disorder). In fact, its first reported use was in 1949,¹ when Dr. John Frederick Joseph Cade, an Australian psychiatrist, found that **lithium** carbonate operated as a mood enhancer in the treatment of manic depression disorder.

This was truly an important discovery because back then, the standard treatments for psychosis were electroshock therapy (a psychiatric treatment in which seizures are electrically induced in anesthetized patients for therapeutic effect) and lobotomy (a neurosurgical procedure, a form of psychosurgery, which consists of cutting the connections to and from the prefrontal cortex, the anterior part of the frontal lobes of the brain).

Horrors! **Lithium** had the distinction of being the first effective medication available to treat a mental illness. Horrah!



Lithium decreases mortality



Last January, we reported on a **lithium** study that heralded one the great advances in longevity for 2011 (see “**Longevity and the Future**” in the January 2011 issue). Researchers from Germany and Japan analyzed the mortality rate in 18 adjacent Japanese municipalities in relation to the amount of the trace element **lithium** contained in tap water from the respective regions.² “We found that the mortality rate was considerably lower in those municipalities with more **lithium** in the drinking water [bold added],” Professor Dr. Michael Ristow, the lead researcher explained.

Longer life from lithium

In other words, a regular small uptake of **lithium** can considerably promote longevity according to the researchers and that even a low concentration of **lithium** leads to an increased life expectancy in humans as well as in a model organism, the roundworm *Caenorhabditis elegans*. In a second experiment, the scientists examined exactly this range of low concentration in the *C. elegans* and were able to confirm: “The average longevity of the worms is higher after they have been treated with **lithium** at this dosage [bold added],” Ristow said. “From previous studies we know already that a higher uptake of **lithium** through drinking water is associated with an improvement of psychological well-being and with decreased suicide rates [bold added],” Professor Ristow continued. If you’re up for a long life, suicide is definitely a downer.

Lithium promotes the formation of new brain cells

Lithium is a brain food, with extraordinary properties, even in small amounts. As Durk Pearson & Sandy Shaw point out (see “**Maintain your Brain the Durk Pearson & Sandy Shaw Way**” in the May 2004 issue):

“One hundred to 150 years ago, we didn’t have the kind of mechanistic medicine that we do now, where we often know what’s going on down at the molecular level. There wasn’t much knowledge, even 100 years ago, about why things went wrong, but there was a lot of empirical knowledge—for example, that nitroglycerin could treat angina. [See “**SUNY’s Nobel sage: NO is beautiful**” on page 11.] That’s interesting, but it was only a decade ago that we finally learned *why* it works (it’s broken down to produce nitric oxide).

“In the case of **lithium**, the first clue that we got came from European health spas. Some mineral springs in Europe acquired the reputation of being able to rejuvenate old people: the springs made them feel better—made them function better—and improved their memories. They generally seemed to restore old people [bold added].”

Especially when they soaked in and drank the spa water for a month or two—long enough that something in the water might have an effect. The Vichy, France spa had a great reputation and its water is still bottled and sold all around the world. It contains 3.5 mg of **lithium** per liter according to Durk & Sandy’s findings and this, they suspect, is a beneficial amount. While it is a common belief that **lithium** must be taken at the level of hundreds of milligrams a day (which may be toxic at those amounts), the evidence continues to grow that it only takes a much smaller amount, say 7 mg/day, to have beneficial effects, and these effects continue to grow over time.

Lithium reduces violent crime

A study published in 1990, conducted over a 10-year period in 27 Texas counties, found that that the incidence rates of suicide, homicide, and rape were significantly higher in counties whose drinking water supplies contained little or no **lithium** than in counties with water **lithium** levels ranging from 70–170 micrograms/L.³ The researchers found that the people getting the higher levels of **lithium** had some beneficial mental effects, even after adjusting for socioeconomic factors, urbanization, etc.

The corresponding associations with the incidence rates of robbery, burglary, and theft were statistically significant. These results suggest that **lithium** has moderating effects on suicidal and violent criminal behavior at levels that may be encountered in municipal water supplies.

When differences in **lithium** consumption were taken into consideration in the Texas counties, the incidences of arrests for possession of opium, cocaine, and their derivatives (morphine, heroin, and codeine) also produced statistically significant inverse associations (less lithium = more arrests, etc.). However, there were no significant associations observed with the reported arrest rates for possession of marijuana, driving under the influence of alcohol, and drunkenness.

In the lithium group, the total positive mood test scores increased steadily during the four weeks of supplementation and specifically in the subcategories reflecting happiness, friendliness, and energy.

Even low-dose lithium has mood-altering effects

Altogether, these results suggest that **lithium** at low dosage levels has a generally beneficial effect on human behavior, which may be associated with the functions of **lithium** as a nutritionally-essential trace element. The lead author, Dr. Gerhard N. Schrauzer, also published a review in which he stated that the available experimental evidence now appears to be sufficient to accept **lithium** as essential, with a provisional RDA for a 70 kg (150 pound) adult of 1 mg/day suggested.^{4*}

* Dr. Schrauzer originally became interested in lithium after growing up next to a “miracle spring” in Franzensbad, Czechoslovakia. (See “**SUNY’s Nobel sage: NO is beautiful**” on page 11.)

Lithium may be good for Alzheimer’s

There have been papers demonstrating that **lithium** can lower the neurotoxicity of amyloid-beta, a major cause of Alzheimer’s disease but the doses have been in the toxicity zone. According to Durk & Sandy, “[W]e’re talking about prevention, where a very small change in toxicity over a long period of time can, like compound interest, plausibly produce some pretty big results years later. Also, researchers have found that **lithium** causes the release of neurotrophic factors that induce neurons to repair themselves and grow rather than die off when they’re under stress ... such as brain-derived neurotrophic factor [BDNF], which is one of the most important for protecting neurons from damage and preventing them from dying. [bold added]”⁵ The same authors have thereafter reported that BDNF plays a critical role in the pathophysiology of mood disorders and in the activity of therapeutic agents in patients with mood disorders.⁶

Lithium found to enhance gray matter

Lithium has also been found to produce an increase in gray-matter portion of the brain consisting mainly of neuronal bodies, which shrinks with age more so than the white matter.⁷ Alzheimer’s disease (AD) actually causes the loss of neurons resulting in gray-matter shrinkage because the number of neurons that are still alive diminishes. So **lithium** may be especially important for AD. In another study, long-term **lithium** treatment was associated with increased gray-matter volumes in the same areas where suicide was associated with decreased volumes.⁸

How does lithium work?

Aside from all of the referenced findings about **lithium** made in “**Lithium** promotes longevity, mood, and love,” to which this sidebar is attached, **lithium** has many other properties. These include its usefulness in the treatment of acute brain injuries such as from ischemia and, aside from Alzheimer’s disease, other chronic neurodegenerative diseases such as Parkinson’s disease, Huntington’s disease, and amyotrophic lateral sclerosis. Also, one of the most important neuroprotective properties of **lithium** is its anti-apoptotic action. Ethanol (drinking alcohol) is a neuroteratogen (a substance that causes malformations in a fetal brain). *Fetal alcohol spectrum disorders* (FASD) are caused by excessive maternal ethanol exposure during pregnancy and these disorders are the leading cause of mental retardation. Exposure to high amounts of alcohol causes *neuroapoptosis* (brain-cell suicide) in the developing brain. Furthermore, ethanol-induced loss of neurons in the central nervous system underlies many of the behavioral deficits observed in FASD. Excessive alcohol consumption is also associated with Wernicke-Korsakoff syndrome and neurodegeneration in the adult brain.

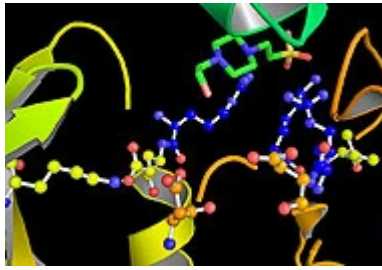


Fig. 1. The active site of GSK-3. The three residues in blue bind the priming phosphate on the substrate, as demonstrated by the ligand. Residues D181, D200, K85, and E97.

Recent *in vivo* and *in vitro* studies indicate that **lithium** is able to inhibit ethanol-induced neuroapoptosis,¹ because it is an *inhibitor of glycogen synthase kinase 3 (GSK3)*, which has recently been identified as a mediator of ethanol neurotoxicity (See Figure 1).

Accordingly, **lithium**'s neuroprotection may result from its inhibition of GSK3. As well, **lithium** also affects many other signaling proteins and pathways that regulate neuronal survival and differentiation. In fact, there is a multitude of recent evidence of **lithium**-mediated protection against ethanol neurotoxicity and potential underlying mechanisms.

Reference

1. Luo J. Lithium-mediated protection against ethanol neurotoxicity. *Front Neurosci* 2010 Jun 28;4:41.

Lithium found to increase neurogenesis, and memory

In the hippocampus, **lithium** was found to create new neurons (neurogenesis).⁹ The hippocampus is the center of memory and the organization of all your memories, and it's one of the few areas of the brain where it's possible for new neurons to grow. So this finding is very important. Another study has recently found that low-dose **lithium** may protect the microstructure of the hippocampus in ultra high-risk for psychosis patients showing that low-dose **lithium** has neuroprotective benefits.¹⁰ In another study, low-dose **lithium** was found to help mice with traumatic brain injury, enhancing spatial learning and memory performance as demonstrated in the Morris water maze test.¹¹

Can lithium contribute to the feelings of new love?

A recent study has found that people with bipolar, depressive, and other psychiatric disorders are far less likely to maintain positive romantic attachments, as demonstrated by subjects with these disorders testing high on anxiety and avoidance scale.¹² From the above references (Schrauzer, 1990; Berger, 2012; Zhe, 2010), we know that low-dose **lithium** can improve mood, and thus reduce anxiety.^{3,10-11}

Also, another study (see "**I'm in the mood for love**" in the November 2012 issue) identified a clear relationship with new love and *nerve growth factor (NGF)* levels,¹³ and **lithium** increases NGF levels. In a recent review,¹⁴ "**Lithium** acts through multiple pathways to inhibit glycogen synthase

kinase-3beta (GSK3 beta). This enzyme phosphorylates and inhibits nuclear factors that turn on cell growth and protection programs, including the *nuclear factor of activated T cells* (NFAT) and [the transcription factor β -catenin in the Wnt pathway]. In animals, **lithium** upregulates neurotrophins, including brain-derived neurotrophic factor (BDNF), [NGF], neurotrophin-3 (NT3), as well as receptors to these growth factors in brain [bold added]." In reference 13, "Notably, there was also a significant positive correlation between levels of NGF and the intensity of romantic love as assessed with the passionate love scale."

Also, according to that review, "**Lithium** also stimulates proliferation of stem cells, including bone marrow and neural stem cells in the subventricular zone, striatum, and forebrain. The stimulation of endogenous neural stem cells may explain why **lithium** increases brain cell density and volume in patients with bipolar disorders [bold added]."

Lithium increases happiness, friendliness, and energy

In a placebo-controlled study with former drug users (mostly heroin and methamphetamines),¹⁵ 24 subjects (16 males and 8 females, average age 29.4 ± 6.5 years) were randomly divided into two groups, one receiving 400 μg of **lithium** per day in yeast, the other a placebo, for four weeks. All subjects completed weekly self-administered mood test questionnaires. In the **lithium** group, the total positive mood test scores increased steadily during the four weeks of supplementation; and specifically in the subcategories reflecting happiness, friendliness, and energy. In the placebo group, the combined mood scores showed no consistent changes; the happiness scores actually declined. **Lithium** is a sure bet to ensure your future, your mood, and perhaps even the love you enjoy!

References

1. Cade JF. Lithium salts in the treatment of psychotic excitement. *Med J Aust* 1949 Sep 3;2(10):349-52.
2. Zarse K, Terao T, Tian J, Iwata N, Ishii N, Ristow M. Low-dose lithium uptake promotes longevity in humans and metazoans. *Eur J Nutr* 2011 Aug;50(5):387-9.
3. Schrauzer GN, Shrestha KP. Lithium in drinking water and the incidences of crimes, suicides, and arrests related to drug addictions. *Biol Trace Elem Res* 1990 May;25(2):105-13.
4. Schrauzer GN. Lithium: occurrence, dietary intakes, nutritional essentiality. *J Am Coll Nutr* 2002 Feb;21(1):14-21.
5. Hashimoto R, Takei N, Shimazu K, Christ L, Lu B, Chuang DM. Lithium induces brain-derived neurotrophic factor and activates TrkB in rodent cortical neurons: an essential step for neuroprotection against glutamate excitotoxicity. *Neuropharmacology* 2002 Dec;43(7):1173-9.
6. Hashimoto K, Shimizu E, Iyo M. Critical role of brain-derived neurotrophic factor in mood disorders. *Brain Res Brain Res Rev* 2004 May;45(2):104-14.
7. Moore GJ, Bebchuk JM, Wilds IB, Chen G, Manji HK. Lithium-induced increase in human brain grey matter. *Lancet* 2000 Oct 7;356(9237):1241-2. Erratum in: *Lancet* 2000 Dec 16;356(9247):2104.
8. Benedetti F, Radaelli D, Poletti S, Locatelli C, Falini A, Colombo C, Smeraldi E. Opposite effects of suicidality and lithium on gray matter volumes in bipolar depression. *J Affect Disord* 2011 Dec;135(1-3):139-47.

9. Chen G, Rajkowska G, Du F, Seraji-Bozorgzad N, Manji HK. Enhancement of hippocampal neurogenesis by lithium. *J Neurochem* 2000 Oct;75(4):1729-34.
10. Berger GE, Wood SJ, Ross M, Hamer CA, Wellard RM, Pell G, Phillips L, Nelson B, Amminger GP, Yung AR, Jackson G, Velakoulis D, Pantelis C, Manji H, McGorry PD. Neuroprotective effects of low-dose lithium in individuals at ultra-high risk for psychosis. A longitudinal MRI/MRS study. *Curr Pharm Des* 2012;18(4):570-5.
11. Zhu ZF, Wang QG, Han BJ, William CP. Neuroprotective effect and cognitive outcome of chronic lithium on traumatic brain injury in mice. *Brain Res Bull* 2010 Oct 30;83(5):272-7.
12. Marazziti D, Dell'osso B, Catena Dell'Osso M, Consoli G, Del Debbio A, Mungai F, Vivarelli L, Albanese F, Piccinni A, Rucci P, Dell'Osso L. Romantic attachment in patients with mood and anxiety disorders. *CNS Spectr* 2007 Oct;12(10):751-6.
13. Emanuele E, Politi P, Bianchi M, Minoretti P, Bertona M, Geroldi D. Raised plasma nerve growth factor levels associated with early-stage romantic love. *Psychoneuroendocrinology* 2006 Apr;31(3):288-94.
14. Young W. Review of lithium effects on brain and blood. *Cell Transplant* 2009;18(9):951-75.
15. Schrauzer GN, de Vroey E: Effects of nutritional lithium supplementation on mood. *Biol Trace Elem Res* 1994;40:89-101.