

## Is lithium potentially a trace element?

Takeshi Terao

Takeshi Terao, Department of Neuropsychiatry, Oita University Faculty of Medicine, Hasama-machi, Yufu City, Oita Prefecture 879-5593, Japan

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**Correspondence to:** Takeshi Terao, MD, PhD, Professor, Department of Neuropsychiatry, Oita University Faculty of Medicine, 1-1 Idaigaoka, Hasama-machi, Yufu City, Oita Prefecture 879-5593, Japan. [terao@oita-u.ac.jp](mailto:terao@oita-u.ac.jp)

Telephone: +81-97-5865823

Fax: +81-97-5493583

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### Abstract

Lithium, a naturally occurring element, is widely used in clinical settings for psychiatric treatment. Several studies showed that micro-dose lithium (*e.g.*, lithium in drinking water) could have anti-aging and anti-dementia effects in addition to an anti-suicidal effect, although anti-manic and psychosis or anti-cancer effects are yet to be determined. Although these studies do not provide conclusive evidence, further studies are warranted to investigate whether lithium is trace element. If so, future studies would need to determine what levels are required to maintain mental health.

**Key words:** Lithium; Trace element; Suicide; Micro-

dose; Aging; Dementia

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**Core tip:** Micro-dose lithium (*e.g.*, lithium in drinking water) could have anti-aging and anti-dementia effects as well as anti-suicidal effect.

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### INTRODUCTION

Lithium, a natural element, is widely used in clinical settings for psychiatric treatment. On the other hand, lithium is taken up by all plants, although it appears not to be required for their growth and development. At high levels in the soil, lithium is toxic to all plants, causing a chlorosis-like condition. Uptake and sensitivity to lithium are species dependent. Consequently, grains and vegetables have 0.5-3.4 mg/kg of lithium, dairy products have 0.5 mg/kg of lithium and meat has 0.012 mg/kg<sup>[1]</sup>. Although there has been a study showing effects of nutritional lithium supplementation on mood<sup>[2]</sup>, no study could directly investigate the association between lithium in the food and mental health. As already pointed out by Schrauzer<sup>[1]</sup>, I wonder whether lithium is one of the trace elements or not. Generally, trace elements are dietary minerals that are needed in very minute quantities for the proper growth, development, and physiology of an organism<sup>[3]</sup>. If lithium is a trace element, various effects may be found at a very low level of lithium concentration?

### TRACE LITHIUM EFFECT ON SUICIDE

With regard to very low lithium levels, there is growing

evidence from epidemiological studies that lithium in drinking water may protect against suicide. An inverse association between lithium levels in drinking water and suicide rates was first reported in the United States for 27 Texas counties<sup>[4]</sup>. In Japan, we showed an inverse association between lithium levels in drinking water and suicide rates for 18 municipalities of Oita prefecture<sup>[5]</sup> whereas another study found no association for 47 subdivisions in the East of England<sup>[6]</sup>. A nationwide Austrian study, however, found an inverse association between lithium levels in drinking water and suicide rates after adjustment for population density, per capita income, proportion of Roman Catholics, as well as the availability of mental health service providers<sup>[7]</sup>.

From 2010 to 2013, we investigated the association in 274 municipalities of Kyushu Island in Japan<sup>[8]</sup>. The association of lithium levels in drinking water with suicide Standardized Mortality Ratios (SMRs) (total, male and female) were investigated thoroughly adjusting for proportion of elderly people, proportion of one person households, proportion of people with college education or more, and proportion of engaging in primary industry, overall unemployment rate, annual marriage rate, annual mean temperature and annual postal savings per person. As a result, lithium levels in drinking water were significantly and inversely associated with male suicide SMRs but not total or female SMRs after the adjustment. The findings suggest that lithium in drinking water may be associated with low risk of male but not female suicide in the general population<sup>[8]</sup>. With regard to gender differences, anti-aggressive effects of lithium could potentially prevent suicide in those who take lithium-contained drinking water for a long time and, if male aggression is greater and more responsive to lithium than female aggression, this could explain the gender effect<sup>[8]</sup>. In any case, such findings support the idea that lithium is a trace element.

With regard to the mechanism, taking the fact into consideration that lithium has been reported to increase the volume of the prefrontal cortex and anterior cingulate gyrus<sup>[9]</sup> it seems likely that lithium may at least partially exert its antisuicidal effect *via* reinforcing "top-down brakes" of aggressive action. Since lithium has been shown to increase the volume and function of the limbic system, such as the hippocampus<sup>[10]</sup>, antisuicidal effects of lithium may consist of both reinforcing "top-down brakes" and decreasing "bottom-up drive." Therefore, lithium may have superior antisuicidal effects relative to other mood stabilizers<sup>[11,12]</sup>.

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## TRACE LITHIUM EFFECT ON MANIA AND PSYCHOSIS

To our knowledge, there has been no reports on effects of lithium as a trace element on mania. This is probably because in a routine psychiatric setting we

prescribe about 600-1000 mg per day of lithium to our patients for producing approximately 0.4-1.0 mEq/L of therapeutic lithium levels for mania, which is much larger than the lithium levels of drinking water.

Nonetheless, there has been a study showing that the incidence of patient's first admissions and prevalence of readmission as well as the diagnosis of psychosis, neurosis, and personality disorder to state mental hospitals from each Texas counties was inversely proportional to the lithium content of their residential drinking water<sup>[13]</sup>. At the moment, trace lithium effect on mania and psychosis is yet to be determined.

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## TRACE LITHIUM EFFECT ON AGING

Interestingly, an inverse correlation was found between lithium levels in drinking water and not only suicide but also all-cause mortality in 18 neighboring Japanese municipalities with a total of 1206174 individuals<sup>[14]</sup>. Taken together with another finding that an exposure to a comparably low concentrations of lithium chloride extended the life span of *Caenorhabditis Elegans*, these findings suggest that long-term low-dose exposure to lithium may exert anti-aging capabilities<sup>[14]</sup>.

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## TRACE LITHIUM EFFECT ON DEMENTIA

Micro-dose lithium may also have efficacy in preventing cognitive loss. For example, 113 patients with Alzheimer's disease were randomized to receive lithium (300 µg/d) ( $n = 58$ ) or placebo ( $n = 55$ ) in a 15-mo, randomized, placebo-controlled, double-blind trial<sup>[15]</sup>. The lithium group showed no decline in performance on the mini-mental state examination test in contrast to the lower scores observed for placebo group, with significant differences starting 3 mo after the beginning of the treatment, and increasing progressively<sup>[15]</sup>.

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## TRACE LITHIUM EFFECT ON CANCER

Although experimental anti-cancer effects of lithium have been shown<sup>[16]</sup>, the range of lithium levels used in the study was 10 mmol/L to 60 mmol/L, which is clearly in the toxic level. Therefore, toxic effects of lithium might have brought about apoptosis in colon cancer cell line. Actually, enhanced but not reduced cancer risk was shown in bipolar disorder patients who were probably receiving long-term lithium treatment<sup>[17]</sup>. At the moment, anti-cancer effects of lithium is yet to be determined.

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## CONCLUSION

These findings suggest that micro-dose lithium (*e.g.*, lithium in drinking water) could have anti-aging and anti-dementia effects in addition to an anti-suicidal effect, although anti-mania and psychosis or anti-cancer effects are yet to be determined. Although

these studies do not provide conclusive evidence, further studies are warranted to investigate whether lithium is trace element. If so, future studies would need to determine what levels are required to maintain mental health. Moreover, although it seems probable that such low levels of lithium in drinking water are far below the levels required to produce aversive and side effects, it is also important to assess side-effects of lithium in drinking water on thyroid function, pregnant women, the unborn, and other potent impairment.

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