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SHORT COMMUNICATION

Low-dose lithium uptake promotes longevity in humans and metazoans

Kim Zarse · Takeshi Terao · Jing Tian · Noboru Iwata · Nobuyoshi Ishii · Michael Ristow

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Abstract
Purpose Lithium is a nutritionally essential trace element predominantly contained in vegetables, plant-derived foods, and drinking water. Environmental lithium exposure and concurrent nutritional intake vary considerably in different regions. We here have analyzed the possibility that low-dose lithium exposure may affect mortality in both metazoans and mammals.
Methods Based on a large Japanese observational cohort, we have used weighted regression analysis to identify putative effects of tap water-derived lithium uptake on overall mortality. Independently, we have exposed *Caenorhabditis elegans*, a small roundworm commonly used for anti-aging studies, to comparable concentrations of lithium, and have quantified mortality during this intervention.
Results In humans, we find here an inverse correlation between drinking water lithium concentrations and all-cause mortality in 18 neighboring Japanese municipalities with a total of 1,206,174 individuals ($\beta = -0.661$, $p = 0.003$). Consistently, we find that exposure to a comparably low concentration of lithium chloride extends life span of *C. elegans* ($p = 0.047$).
Conclusions Taken together, these findings indicate that long-term low-dose exposure to lithium may exert anti-aging capabilities and unambiguously decreases mortality in evolutionary distinct species.

Keywords Trace elements · Lithium · Mortality · Longevity · Human · *C. elegans*

K. Zarse · J. Tian · M. Ristow (✉)
Department of Human Nutrition, Institute of Nutrition, University of Jena, D-07743 Jena, Germany
e-mail: mristow@mristow.org

T. Terao · N. Ishii
Department of Neuropsychiatry, Oita University Faculty of Medicine, Oita, Japan

N. Iwata
Department of Clinical Psychology, Hiroshima International University, Hiroshima, Japan

M. Ristow
Department of Clinical Nutrition, Institute of Human Nutrition, Potsdam-Rehbrücke, Germany

Introduction

Lithium (Li^+) is a nutritionally essential trace element found predominantly in plant-derived foods and drinking water [1, 2]. Environmental Li^+ exposure and concurrent intake vary considerably from region to region [2, 3].

The trace element Li^+ is typically present in all human organs and tissues, and is equally distributed in body water, while Li^+ is absorbed from the intestinal tract and excreted by the kidneys [2]. Whereas deficiency of Li^+ causes behavioral abnormalities and reduced litter size in rats, defined human Li^+ deficiency diseases are unknown [2].

While the physiological functions of Li^+ are mostly unresolved, high-dose lithium chloride (LiCl) is widely used to treat psychiatric conditions like bipolar disorder since 1949 [4–6]. Additionally, nutritional Li^+ uptake may affect mental health in humans at sub-pharmacological, i.e. low micromolar doses. In particular, environmental Li^+ exposure may be associated with reduced suicide rates [2, 7, 8]. We now have analyzed whether environmental low-dose Li^+ exposure may affect mortality in a large Japanese cohort, and have additionally tested whether comparably low concentrations of Li^+ may affect life span of a model

organism for anti-aging studies, the roundworm *Caenorhabditis elegans*.

Subjects, materials and methods

Observational cohort

All methods and materials related to the human sample have been previously described [8]. This study is based on the population of Oita prefecture in the year 2006, at that time totaling 1,206,174 individuals that are distributed over 18 municipalities with differing individual population sizes.

Standardized mortality ratios

Taking the difference in gender and age distribution of individual municipality populations into account, the standardized mortality ratio (SMR) was calculated for each individual municipality. SMR is an indirect method of adjusting a mortality rate, defined as the number of observed deaths in an individual municipality population divided by the number of expected deaths, compared with the gender- and age-matched general population [8].

Tap water lithium levels

Lithium levels in the tap water suppliers of each municipality were measured using ion chromatography at Oita City Waterworks Bureau or by using mass spectroscopy at Oita Yakuzaishi Kensa Center [8]. Both methods have a sensitivity of 0.1 mg/L. Lithium levels of drinking water were measured at multiple water suppliers in the same municipality, and the median value was calculated for each municipality. Although lithium levels were typically measured only once per supplier, we observed a very small time-dependent fluctuation in concentrations: the correlation coefficient between the lithium levels and those re-quantified after one year in the same places was 0.998.

The distribution of median lithium levels was considerably skewed (skewness = 3.39; kurtosis = 12.80). We thus had to employ logarithmic transformation (thereafter: skewness = 0.002; kurtosis = 0.075) before applying parametric statistical procedures. Because of considerable differences in population size across the 18 municipalities, weighted least squares regression analysis, adjusted for the size of each population, was used to investigate the association of lithium levels in drinking water and the SMRs [8].

C. elegans life span analysis

The *C. elegans* strain used was Bristol N2. All experiments were performed exactly as previously described [9] except that streptomycin and 5-fluoro-2′-deoxyuridine were omitted, and synchronization was performed using an overnight egg-laying period (i.e. without applying bleach to eggs), as previously described elsewhere [10]. Living *E.coli* OP50 bacteria were used as the only food source. Analytical grade lithium chloride was purchased from Sigma–Aldrich (Munich, Germany).

Results

Analyzing overall mortality data from 1,206,174 individuals in Oita prefecture of Japan regarding their possible correlation with drinking water Li^+ concentrations, we find that tap water Li^+ levels in the 18 municipalities within the Oita prefecture are inversely associated with overall mortality rates adjusted for gender and age ($\beta = -0.661$, $p = 0.003$) (Fig. 1a). We additionally adjusted for suicide rates in this prefecture, since these have been previously shown to be negatively associated with tap water Li^+ levels in this particular cohort [8]. After additional adjustment for suicide, overall mortality was still inversely associated with

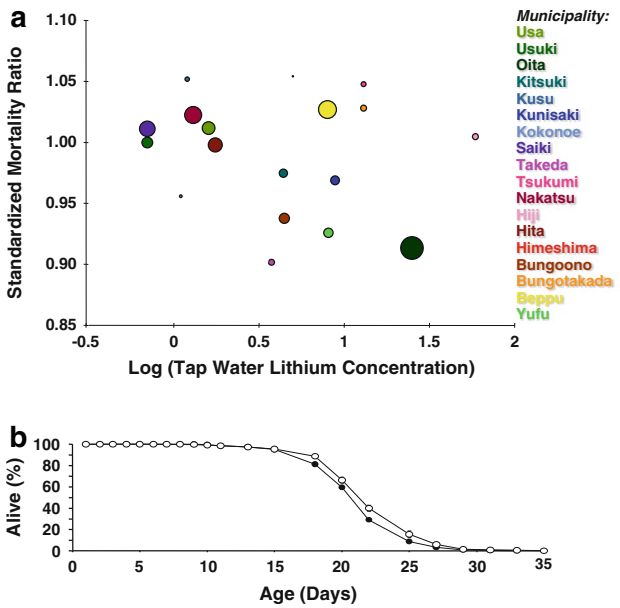

Fig. 1 Low-dose lithium exposure modulates mortality. **a** depicts data from 18 different Japanese municipalities which are named and color coded on the *right-hand side*. The numbers of inhabitants are reflected by the respective diameter of *circles*. The *X*-axis shows logarithmic median tap water lithium concentration, the *Y*-axis depicts the standardized mortality ratio, defined as number of observed deaths divided by the number of expected deaths. **b** depicts are mean values (±SEM) of three separate experiments with approximately one hundred of *C. elegans* roundworms per experiment and condition. *Black circles* reflect control animals, *open circles* reflect animals that were continuously exposed to 10 μM lithium chloride

tap water Li^+ levels ($\beta = -0.580$, $p = 0.037$) (data not depicted). This inverse correlation suggests that Li^+ exposure may contribute to reduced overall mortality in humans independent of suicide risk.

LiCl has been previously shown to extend life span of a model organism for anti-aging studies, the roundworm *Caenorhabditis elegans*, when applied at high, i.e. non-nutritional doses of 5 mM and above [11]. However, drinking water Li^+ concentrations in the Oita prefecture ranged from 0.7 to 59 μg/L only [8], the latter equaling a concentration of 8.5 μM. Hence, we have continuously exposed several hundreds of *C. elegans* in separate experiments to 1 and 10 μM LiCl, respectively. We found mortality in populations exposed to 10 μM of LiCl to be decreased ($p = 0.047$) (Fig. 1b), while a concentration of 1 μM of LiCl had no detectable effect on *C. elegans* life span (data not shown).

Discussion

Our findings indicate that low-dose Li^+ exposure causes reduced mortality in *C. elegans*, and that these life span-extending capabilities of low-dose Li^+ can be observationally translated into reduced overall mortality in humans that have been exposed to comparable amounts of Li^+ in a similar long-term fashion.

It should be noted, however, that the findings in humans are observational and hence cannot provide a causal link between high-level Li^+ intake on the one hand, and reduced mortality on the other hand. On a theoretical basis, a life-long intervention study in humans would be required to provide causal evidence for mortality-reducing effects of low-dose lithium supplementation. Such a study, for obvious reasons, cannot be materialized.

Hence, we used a typical model organism for anti-aging studies, *C. elegans*, to test whether low-dose Li^+ levels similar to those observed in some areas of the Oita prefecture, i.e. 10 μM, may actually *cause* reduced mortality. Based on previously published evidence from the Lithgow laboratory, a 1000-fold higher concentration extends *C. elegans* life span by 36% also by reducing expression of the *C. elegans* ortholog of a histone demethylase named LSD-1 in mammals and T08D10.2 in *C. elegans*, respectively. It hence is of little surprise that the concentration employed in the current study exerts less pronounced effects on life span of *C. elegans*. However and most importantly, this low concentration *causes* reduced mortality, suggesting that the effects of a similar exposure of humans within the Oita prefecture in regard to reduced mortality are not a mere coincidence, but rather reflect unresolved molecular effects on human mortality that clearly require further investigation.

Lastly and given the long-standing psychiatric experience with high-dose Li^+ supplementation in humans, these findings raise the possibility that readily available low-dose Li^+ supplementation at non-toxic doses may not only promote mental health and impair suicide risk [2, 7, 8] but also may reduce overall mortality in humans.

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References

1. Anke M, Arnhold W, Groppel U, Krause U (1991) The biological importance of lithium. In: Schrauzer GN, Klippel KF (eds) Lithium in biology and medicine. VCH Verlag, Weinheim, pp 149–167
2. Schrauzer GN (2002) Lithium: occurrence, dietary intakes, nutritional essentiality. J Am Coll Nutr 21:14–21
3. Zaldivar R (1980) High lithium concentrations in drinking water and plasma of exposed subjects. Arch Toxicol 46:319–320
4. Cade JF (1949) Lithium salts in the treatment of psychotic excitement. Med J Aust 2:349–352
5. Cipriani A, Pretty H, Hawton K, Geddes JR (2005) Lithium in the prevention of suicidal behavior and all-cause mortality in patients with mood disorders: a systematic review of randomized trials. Am J Psychiatry 162:1805–1819
6. Rapoport SI, Basselin M, Kim HW, Rao JS (2009) Bipolar disorder and mechanisms of action of mood stabilizers. Brain Res Rev 61:185–209
7. Schrauzer GN, Shrestha KP (1990) Lithium in drinking water and the incidences of crimes, suicides, and arrests related to drug addictions. Biol Trace Elem Res 25:105–113
8. Ohgami H, Terao T, Shiotsuki I, Ishii N, Iwata N (2009) Lithium levels in drinking water and risk of suicide. Br J Psychiatry 194:464–465
9. Schulz TJ, Zarse K, Voigt A, Urban N, Birringer M, Ristow M (2007) Glucose restriction extends *Caenorhabditis elegans* life span by inducing mitochondrial respiration and increasing oxidative stress. Cell Metab 6:280–293
10. Lithgow GJ, White TM, Melov S, Johnson TE (1995) Thermotolerance and extended life-span conferred by single-gene mutations and induced by thermal stress. Proc Natl Acad Sci USA 92:7540–7544
11. McColl G, Killilea DW, Hubbard AE, Vantipalli MC, Melov S, Lithgow GJ (2008) Pharmacogenetic analysis of lithium-induced delayed aging in *Caenorhabditis elegans*. J Biol Chem 283:350–357