Medical Hypotheses 115 (2018) 94–102

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Psychiatric benefits of lithium in water supplies may be due to protection from the neurotoxicity of lead exposure

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ABSTRACT

Introduction: Lithium is a medication used to treat bipolar disorder and may also prevent cognitive decline and suicide. Lithium is also found naturally, in levels well below clinical doses, in drinking water worldwide, and levels have been inversely associated with rates of psychiatric disorders. Lead (Pb) is another element in the environment but is a toxin of public health concern. Negative effects of chronic lead exposure and possible benefits of environmental lithium exposure appear complementary.

Hypothesis: Exposure to environmental lithium has associated benefits, which may be due to the mitigation of lead toxicity by lithium.

Methods: A series of reviews tested each element of the hypothesis. A systematic review clarified the psychiatric and medical correlates of lithium in drinking water. Non-systematic reviews clarified the harms of environmental lead, summarized experimental studies of lithium used to prevent lead toxicity, and explored overlapping biological mechanisms in lithium and lead exposure.

Results: Higher levels of lithium in drinking water were associated with lower suicide rates in 13 of 15 identified studies. While fewer studies were available for other outcomes, lithium was associated with lower rates of homicide, crime, dementia, and mortality. Lead was reported to be ubiquitous in the environment, and chronic low-level exposure has been associated with adverse effects, including effects opposite to the outcomes associated with lithium. Animal studies demonstrated that lithium pre-treatment mitigates lead toxicity. Neurophysiological correlates of lead and lithium exposure overlap.

Conclusions: Microdose lithium is associated with better psychiatric and medical outcomes, which are complementary to harms of environmental lead exposure. Experimental animal evidence is supportive, and lead and lithium impact overlapping neurophysiologic pathways. Therefore, several lines of circumstantial evidence suggest that lithium protects against the neurotoxic effects of lead. Further studies are required to clarify the benefits and mechanisms of low-dose lithium. There are significant public health implications if this paper's hypothesis is true.

Introduction

Lithium, the third element on the periodic table, is an established medication. It is a mood stabilizer: a first-line treatment for bipolar disorder [1], and it is also used in unipolar depression. Treatment with lithium reduces the risk of suicide across psychiatric diagnoses, with high quality evidence in bipolar disorder and unipolar depression [2]. Clinically, typical doses may range from 600 mg to 1800 mg per day and individual doses are based on clinical effect, side effects, and blood levels [3,4]. At lower doses, lithium may also reduce the progression to dementia from mild cognitive impairment [3].

Not only found in the medicine cabinet, lithium is abundant in the Earth's crust. Present in minerals in varying amounts in different regions, lithium dissolves into groundwater and is commonly found in drinking water. In turn, lithium is consumed by humans who drink the water and eat the grains and vegetables that take it up [5]. Daily intake of lithium therefore ranges by location and diet, with estimates of mean daily intake in the range of 348–1560 μg/day (0.348–1.560 mg/day) [5], i.e. two to three orders of magnitude lower than effective clinical doses (see Fig. 1 for visualization).

Nonetheless, mounting evidence from epidemiological studies that correlate drinking-water lithium levels with health outcomes suggests that exposure to microdose environmental lithium may be beneficial. For example, higher drinking water concentrations are shown to

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https://doi.org/10.1016/j.mehy.2018.04.005
Received 14 January 2018; Accepted 10 April 2018

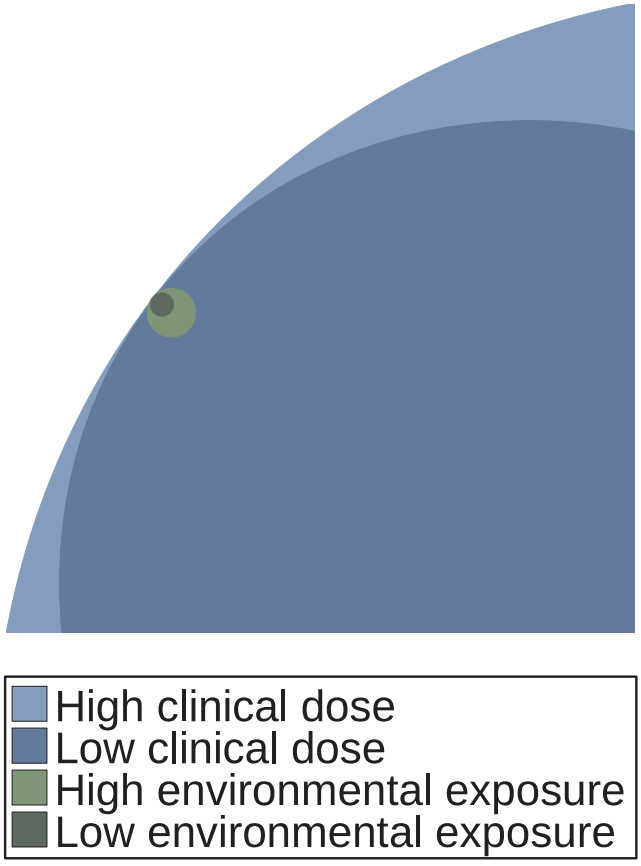

Fig. 1. Relative size comparisons of clinical lithium doses[3] compared to estimated mean environmental daily intake[5], represented with dose proportional to circle areas.

correlate with lower rates of suicide, homicide, and dementia [6,7].

Despite its status as an established effective medication, the mechanism underlying the clinical benefits of lithium is uncertain [8]. Lithium has broad effects on cellular signalling pathways in the brain involving glycogen synthase kinase 3 (GSK-3), cyclic adenosine monophosphatase response element binding protein (CREB), and Na^+-K^+ adenosine triphosphatase (ATPase), with influences on calcium homeostasis [8]. The beneficial mechanism of action may differ in different populations [8]. As with bipolar disorder, the mechanism of the purported beneficial effects of microdose lithium is uncertain [3].

Meanwhile, lead is described as ubiquitous in the environment in varying amounts, detectable even in regions of the arctic [9]. Lead is noted to be a "cumulative general poison", and is neurotoxic [9]. The Centre for Disease Control reports that for children, no safe lower limit of lead blood level has been found [10]. Lead toxicity is a global public health problem: 0.2% of deaths and 0.6% of disability-adjusted life years are attributed to lead exposure, surpassing urban outdoor air pollution and climate change [11].

Hypothesis

A parsimonious mechanistic explanation of the effects of microdose lithium would account for the breadth of its apparent effects. A possible clue to that mechanism may be in the broad and complementary effects of lead, another environmental element. We hypothesize that if the harms of lead exposure are opposite to the benefits of lithium exposure, then the benefits of lithium may be due to mitigation of the toxicity of lead. This possibility is important to clarify, as it would have implications on any recommendations to supplement lithium.

The hypothesis would be supported if: the harms of lead are opposite to the benefits of lithium; lead and lithium co-occur in the environment where such harms and benefits are observed; lead and lithium have effects on shared biological processes; there is experimental evidence demonstrating lithium mitigates the neurotoxicity of lead. The aim of this paper is to review the literature for evidence supporting or refuting these empirical possibilities in order to clarify the relationship and determine the next steps that may be required.

Methods

This paper aims to explore the hypothesis that lithium mitigates the negative health impacts of lead. First, in Part 1, a systematic review was done to identify the health outcomes associated with environmental lithium exposure. Second, in Part 2 the health risks of lead exposure were reviewed. Third, potential causal connections between lithium and lead were identified by reviewing experimental studies (Part 3). And finally, potential areas of overlap in the mechanisms of action in lithium and lead were identified by highlighting physiologic and biologic studies (Part 4).

Part 1: Systematic review of the health impacts of exposure to environmental lithium

Literature search

A systematic search was completed using MEDLINE with the PubMED interface on November 16, 2017 with the following query: ((“lithium”[MeSH Terms] OR “lithium”[All Fields]) AND (“water”[MeSH Terms] OR “water”[All Fields] OR “drinking water”[MeSH Terms] OR (“drinking”[All Fields] AND “water”[All Fields]) OR “drinking water”[All Fields])). The human filter was applied. By using the human filter, articles that have not yet been indexed with MeSH subheadings are excluded, so there is a risk of missing the most recently published articles. Therefore, the search was repeated without the filter to identify potential recent articles from January 1, 2017 to November 16, 2017. These articles were combined with the first search and duplicates removed.

Entries were included if they described a peer-reviewed, primary literature study that reported on a direct or indirect measure of drinking water lithium and a psychiatric or non-psychiatric medical outcome. The rationale for considering all health outcomes is the arbitrary distinction between mental and medical illness, as well as the potential impact of medical problems on illnesses categorized as psychiatric (for example the impact of thyroid diseases on mood disorders and vascular disease on cognitive disorders). Entries were excluded if they did not contain an abstract; were not in English; or were reviews (which were separately retrieved for background and to identify any missed primary articles), commentaries, letters, or hypotheses if they did not contain original data. Interventional studies that administered lithium as a treatment were excluded.

Part 2: What are the psychiatric impacts of environmental lead exposure?

Compared to the potential benefits of exposure to environmental lithium, lead toxicity is an established fact in the medical and scientific literature and a topic of great importance to public health. Therefore, for efficiency and accuracy, Part 2 relied on previously-published, recent high-quality reviews. A non-systematic search for recent scoping reviews from governmental and non-governmental bodies such as the World Health Organization (WHO) and the government of Canada was completed. The reviews were read and summarized to answer specific questions relating to the hypothesis. When there was insufficient information in the identified reviews, primary source literature was used to answer the question and critically appraise the articles individually.