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Guest Editorial

Lithium orotate: distinct compound or simply Li^+ after administration?

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Summary

The recent study by Aron et al about lithium deficiency and the onset of Alzheimer's disease provides a valuable explanatory framework for understanding how very small doses of lithium, delivered via environmental exposure, can exert neuroprotective effects. It also contains results which will need to be reconciled with foundational chemistry and existing evidence and which could be potentially misleading. The suggestion that lithium orotate (LiO) exhibits benefits relative to the more traditionally used lithium carbonate (LiC) requires further scrutiny in light of the following arguments: (a) no study has demonstrated the presence of stable LiO in physiological fluids; (b) acid–base chemistry predicts that LiO will be largely protonated in the stomach, causing it to dissociate and be absorbed as Li^+; (c) experimental studies indicate that LiO and LiC have comparable pharmacokinetics after oral administration; and (d) previous research has shown that LiC also has neuroprotective effects, including at very low doses. Disproportionate focus on a specific lithium salt could have safety implications and may distract from answering fundamental questions about the effects of very low doses of lithium. More experiments are needed to provide evidence of a stable LiO complex in physiological fluids before this becomes the main form of lithium in future clinical trials.

Keywords

Lithium; lithium orotate; lithium carbonate; neuroprotection; prevention.

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The recent study by Aron et al[1] demonstrated the opposing effects of lithium depletion versus low dose supplementation on brain ageing and the pathology of Alzheimer's disease. This provides a valuable explanatory framework for understanding why very small doses of lithium, such as those delivered via environmental exposure, could exert neuroprotective effects. The authors also found that at very low, microgram doses, lithium orotate (LiO), demonstrated more pronounced neuroprotective effects than lithium carbonate (LiC). These findings appear robust across multiple experimental end-points; however, the mechanism of these effects remains uncertain. Aron et al explained this difference by the lower affinity of LiO to be sequestrated into amyloid plaques. This would require that after ingestion, LiO enters the bloodstream as an intact complex. Yet, (a) no study has demonstrated the presence of stable LiO in physiological fluids; (b) acid–base chemistry predicts that LiO will be largely protonated in the stomach, causing it to dissociate and be absorbed as Li^+; (c) experimental studies indicate that LiO and LiC have comparable pharmacokinetics after oral administration; and (d) previous research has shown that LiC also has neuroprotective effects, including at very low doses.

Prior to the Aron et al study, we could not explain why environmental exposure to lithium, which is substantially lower than clinical dosing, was associated with lower rates of dementia.[1,2,a] Aron et al showed the neuroprotective effects of lithium administered in drinking water at levels of 30 μg/L of elemental lithium which are well within the range of levels found in the water supply. Thus, neuroprotective effects were demonstrated after very long treatment (30–40% of the lifespan of mice), but with only very low doses, well below the doses where side-effects are likely. This opens the field to testing of long-term treatment with subclinical and even microdoses of lithium, thus reducing safety concerns. All in all, the renewed focus on the neuroprotective effects of lithium, sparked by the findings of Aron et al,[1] is both timely and necessary. We applaud the authors for a very impressive body of experiments. At the same time, the results relating to LiO require additional scrutiny.

Aron et al[1] in vitro tested 16 different lithium salts for amyloid-binding affinity. Lithium orotate showed the weakest binding to amyloid plaques compared with LiC and other salts (e.g. acetate, chloride, citrate). After seven days of treatment with low-dose lithium in plaque-bearing Alzheimer's disease model mice, LiO treated groups had higher parenchymal brain lithium and lower plaque to non-plaque lithium ratios than the LiC group. Aron et al[1] then went on to test lithium supplementation in vivo. In separate cohorts from the lithium depletion experiments, they showed that equivalent and very low doses of lithium administered for 7–9 months as either LiC or LiO in drinking water, resulted in comparable serum and hippocampal lithium levels, but demonstrated different effects on the brain in mice. Specifically, in cross-sectional comparisons, LiO treatment, compared with both LiC treated and untreated (plain water) controls, resulted in lower Aβ plaque burden, lower phospho-tau+ cell density and better memory performance in Alzheimer's disease mice, and lower gliosis, higher synapse density and better memory performance in wild-type mice.

Aron et al[1] explained the LiO versus LiC difference by postulating that LiO has a lower affinity to bind amyloid and get sequestered into plaques in vivo, thus maintaining higher bioavailable lithium in non-plaque neuropil, which then more effectively engages with protective pathways. It is of note that they only measured the plaque/non-plaque ratios after 7 days of treatment, which may not be long enough to establish stable ratios. Interestingly, there were also earlier, but unconfirmed, suggestions that LiO differs from other lithium salts. Hans Nieper suggested that

a There are also many environmental studies showing association between very low, environmental levels of lithium and other clinical outcomes – suicide, psychiatric hospitalisations, violent crime. While some of the mechanisms described in the Aron et al[1] study may also be relevant to these outcomes, as the *Nature* paper did not directly study these outcomes, we will not focus on them either.

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circulating LiO undergoes 'directed intracellular transport' facilitated by orotate as a carrier, releasing lithium only at the intracellular site of action. It is important to note that the differences between LiO and other lithium salts in both explanations relate to pharmacokinetics. The hypothesis is that orotate effectively serves as a bioavailability enhancer, which increases absorption and distribution of lithium according to Dr Nieper and/or prevents sequestration of lithium into amyloid plaques according to Aron et al. Regardless of the form of administration, it is ultimately lithium that exerts the multitude of biological effects. Indeed, Aron et al tested this and showed no effect of orotate itself on neuroprotection.

As in both explanations orotate serves as a bioavailability enhancer, LiO could differ from LiC only if it is absorbed and circulated as LiO not just as Li^+. Yet, the existence of stable LiO in blood following per os administration was not demonstrated in the Aron et al[1] study or any other study. In general, lithium salts, including organic ones, freely dissociate in aqueous or physiological fluids because the small, monovalent Li^+ ion is strongly stabilised by hydration. Crystallography data demonstrate that LiO is a contact ion pair arrangement not a covalent bond or a chelate. Furthermore, when administered per os, LiO must pass through the stomach. Following acid base chemistry and the Henderson–Hasselbalch equation, when mixed with a stronger acid, such as gastric hydrochloric acid, the conjugate base that binds lithium (HOr^-) is converted to orotic acid (H_2Or). Orotic acid loses its negative charge. As a result, lithium ions dissociate and become free in solution. Under certain conditions, such as following food intake, the gastric pH will increase and, in that case, a smaller proportion of LiO would be protonated. Regardless, the proportion of HOr^-, which can bind cations depends on the gastric pH and is often negligible. In the intestine, lithium remains soluble and is absorbed as Li^+. In the blood, sodium$^+$, calcium^{2+}, magnesium^{2+} and potassium$^+$ which are present at several orders of magnitude higher concentrations would be expected to outcompete Li^+ in rebinding to any remaining deprotonated orotate. Importantly, for the in vitro amyloid binding experiments, Aron et al dissolved LiO in pure water, not physiological solution where competing ions could disrupt LiO contact ion pairs and increase the free Li^+ fraction. All in all, current evidence suggests that after ingestion, LiO, same as LiC, is predominantly absorbed and circulated as Li^+.

If LiO entered the bloodstream as such, it should have different pharmacokinetics than LiC. The early suggestions for differential pharmacokinetics of LiO and LiC emerged from studies using peritoneal administration, not per os treatment. Later experimental evidence showed that the pharmacokinetics of LiC and LiO are in fact comparable when administered orally. Smith et al[3] administered LiO, LiC or lithium chloride (LiCl) to rats via food for 20 days, incrementally increasing the lithium concentration. No differences were observed between LiO, LiC and LiCl in lithium absorption, distribution and urinary excretion after short-term or long-term administration. Plasma and brain lithium concentrations were nearly identical among all three compounds at each measurement point. In keeping with this, Aron et al[1] also found that in mice, equivalent doses of lithium administered as either LiC or LiO in drinking water, resulted in comparable serum and hippocampal lithium levels. The replicated evidence from animal experiments showing comparable pharmacokinetics of LiC and LiO after ingestion does not support the explanation that these two salts circulate in different forms.

Separate from the pharmacokinetics, there is extensive evidence that LiC or Li^+ also exert neuroprotective effects even at very low doses. Specifically, microdoses of lithium, i.e. ~1.17 µg of lithium per day, administered for 16 months as LiC per os in mice resulted in a decreased number of senile plaques, no neuronal loss in the cortex and hippocampus and increased brain-derived neurotrophic factor density in the cortex, when compared with non-treated mice.[4] When it comes to human studies, concentrations of lithium in drinking water as low as 10.1 µg/L, are associated with lower risk of dementia in several studies,[2] yet environmental exposure is not to LiO. Natural sources of lithium are predominantly inorganic and based on PH REdox EQuilibrium in C language modelling,[b] lithium in drinking water exists almost entirely as the hydrated monovalent cation Li^+. There is also evidence that microdoses (300 µg) or subtherapeutic doses of LiC slow cognitive decline in Alzheimer's disease or amnestic mild cognitive impairment (aMCI), increase cerebrospinal fluid amyloid-beta peptide (Aβ1-42) and reduce phosphorylated tau in aMCI.[5–7] Importantly, none of the studies demonstrating positive effects of lithium on brain structure used LiO; instead, they primarily used LiC, albeit at much higher, clinical doses.[8] All in all, there is a replicated and growing body of evidence that other forms of lithium administered at subtherapeutic doses also exert neuroprotective effects. This may not be a unique effect of LiO, but rather a general effect of long-term exposure to lithium regardless of the specific salt. Any studies testing LiO in humans should include a LiC control group, to differentiate between whether any observed effects are specific to LiO or broadly related to Li.

What other explanations could there be for the difference between LiO and LiC in the Aron et al study? LiC tastes more bitter/metallic, which may subtly reduce voluntary water consumption in mice compared with LiO. The authors stated that water intake and serum lithium levels were not significantly different after treatment, but with between 8 and 17 animals per group, the study was likely underpowered to demonstrate significant between-group differences in these measures. More importantly, a single measure of lithium levels does not adequately quantify the overall lithium exposure. Even small differences in water intake or in single time point lithium levels, could compound into substantially lower cumulative lithium exposure over the 7–9 months of the study (area under the curve) for the LiC arm, which could explain the lower efficacy. Furthermore, in mice, the stomach is much less acidic than in humans, therefore there may be less dissociation of LiO. Consequently, it is unclear whether the effects of LiO as observed in rodents would translate to human participants.

While the increased interest in lithium is well justified, there is a concern that the over-the-counter and especially over-the-internet availability of LiO, combined with growing enthusiasm, could lead to overdoses. In 1948, the use of lithium as a salt replacement in people with hypertension resulted in toxic side-effects and even fatalities, which for years had an impact on the therapeutic use of lithium in bipolar disorder. Repeating this history would be very unfortunate. The toxicity of lithium in these instances was potentiated by sodium depletion, which led to greater reabsorption of lithium in the kidneys. Thus, use of over-the-counter or over-the-internet purchased lithium without any medical supervision is potentially dangerous, in general, and especially in certain populations. This raises concerns that misuse of over-the-internet bought LiO could negatively affect future research in this area. Indeed, there is already at least one reported case of acute lithium toxicity after ingestion of LiO purchased over the internet.[9] The patient intentionally took 18 tablets of a product containing LiO, an equivalent of 440 mg of LiC. Lithium levels in this patient never exceeded 0.4 mmol/L, which is similar to levels one would expect with equivalent dose of LiC and close to the therapeutic range (0.6 mmol/l in adults, but 0.4 mmol/l in elderly patients). While the symptoms were relatively mild (nausea, vomiting, tremor),

b PHREEQC version 3, MacOS (OS 10.7–10.12), US Geological Survey (USGS); https://www.usgs.gov/software/phreeqc-version-3.

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they are similar to symptoms one would expect with rapid initiation of LiC treatment at an equivalent dose. Therefore, it is quite possible to reach clinical doses and demonstrate side-effects with the over-the-internet purchased lithium supplement – some supplements provide up to 20 mg of elemental lithium per dose, which is equivalent to ~100 mg of LiC.

Considering the previous literature and the chemical properties of lithium salts, the differences between LiC and LiO in humans may be negligible. The available evidence suggests that regardless of the form, long-term ingestion of lithium, even at low doses, may be neuroprotective. More experiments are needed to demonstrate a stable LiO complex in physiological fluids following per os administration, before this becomes the main form of lithium in future clinical trials. Rather than focusing on a specific lithium salt, we should clarify some key outstanding questions first. For example, we do not even know the affinities and half-maximal effective and inhibitory concentrations of lithium for relevant neuroprotective targets. A disproportionate focus on LiO may distract from answering these more fundamental questions about the effects of very low doses of lithium and could have safety implications.

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Declaration of interest

None.

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