Lithium: new observations on an old medication

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Lithium is undoubtedly a unicum in the field of pharmacology [1]. Its distinct profile of clinical effectiveness, that reaches peak levels in the prevention of recurrences and reduction of suicide risk in mood disorders [2,3], is complemented by a pleiotropic molecular mechanism that produces vast perturbations in inter- and intra-cellular signaling. This small ion, administered in humans as a salt, exerts predominantly effects at the level of second and third messenger systems, determining significant modulations of the expression of target genes [4]. Lithium decreases apoptotic processes, facilitates autophagy, ultimately increasing cell and neuronal survival. The latter mechanisms appear to underlie lithium-driven moderation of cellular neurodegenerative processes observed in Alzheimer's disease, amyotrophic lateral sclerosis, frontotemporal dementia, and Parkinson's disease [5]. Interestingly, neuroprotective effects of lithium appear to be biologically evident not only at microscopic levels in the CNS, but also structurally, with counteraction of the widespread cortical thinning and reduced hippocampal volume observed in large-scale neuroimaging studies of patients affected by bipolar disorder [6]. A final remark concerns the evidence that clinical response to lithium is, at least in part, genetically determined [7,8]. This evidence seems to correspond to the presence of a distinct phenotypic signature that is associated with, and predicts [3], better clinical outcome during lithium treatment. Finally, lithium has shown antiviral activity, and this has been associated to a decreased risk of infection with Sars-Cov-2 possibly in relation to its serum levels [9]. In this context, it appears timely to summarize recent findings of pre-clinical (cellular and animal models) and clinical research on the effects of lithium, with a focus on precision approaches, i.e. the application of individualized management of lithium therapy. This special issue entitled "Lithium: new observations on an old medication" presents an overview of the most recent molecular and translational findings in lithium's research. The paradoxical decrease of lithium use worldwide despite its proven efficacy (and effectiveness) on a number of clinical conditions has been highlighted by Rybakowski and Ferensztajn-Rochowiak [10]. The authors call for increased training and education among mental health providers to promote lithium use in light of its evident antisuicidal, antiviral and neuroprotective effects. Importantly, promoting a correct use of lithium would also decrease the likelihood of developing side effects, ultimately leading to a larger number of mood disorder patients as beneficiaries of its properties [10]. The mini-reviews from Singulani et al. [11], Salarda et al. [12], and Haussman et al. [13] discuss, from different angles, data pointing to the

neuroprotective properties of lithium. Indeed, Singulani et al. [11] showed that the mitochondria modulating properties of lithium could underlie part of its neuroprotective and neurotrophic effects. This could be relevant in neurodegenerative disorders such as Alzheimer's disease (AD) where mitochondrial dysfunction likely plays a fundamental role. The authors suggest that the beneficial effects of lithium on mitochondrial function, possibly determined by a combination of activation of the Wnt signaling pathway, via inhibition of the GSK-3β, as well as through mechanisms that act directly on transcriptional pathways related to mitochondrial integrity, should be further investigated in preclinical studies [11]. Furthermore, Salarda et al. [12] focused on the possible molecular effects of lithium as an anti-aging agent. To this end, they collected evidence on the anti-aging mechanisms associated with lithium use in bipolar disorder, which is characterized neurobiologically by shortened telomeres, increased oxidative stress, and accelerated epigenetic aging [12]. Despite promising results, the elucidation of the exact mechanism by which lithium may act as an anti-aging agent and the extent to which these mechanisms are relevant to its mood stabilizing properties in BD need to be further investigated [12]. Finally, Haussman et al. [13] summarized experimental and clinical data revealing that lithium is capable of attenuating Alzheimer's disease pathology and stimulating adult hippocampal neurogenesis. Cumulatively, data suggest that lithium might be a therapeutic option in the treatment of Alzheimer's disease and its prodromal stages. However, the authors call for properly designed clinical studies, including head-to-head comparisons with approved dementia treatment options, to assess lithium efficacy in this population of patients [13]. Another set of papers focused on the genomic [14] and epigenetic [15] determinants of clinical response to lithium. Specifically, Papiol et al. [14] offered a perspective on the recent advancement in the comprehension of the genomic architecture of lithium responsive bipolar disorder. This trait appears indeed to be polygenic although multiancestry analysis are lacking samples. The authors highlight how the integration of multiple omics data, and their combination with advanced machine learning techniques hold promise for the understanding of the complex biological underpinnings of lithium treatment response [14]. Further, Marie-Claire et al. [15] systematically analyzed the literature on the epigenetics effects of lithium. There is indeed substantial evidence supporting the involvement of environmental factors as modulators of lithium response. This has resulted in a significant amount of work, using different analytical approaches in different models and tissue types, showing that

lithium might enact epigenetic modifications through methylation, miRNA and histone modifications [15]. However, studies combining diverse epigenetic mechanisms or integrating transcriptomics and epigenetics are scant. The analysis of adequately powered, and carefully characterized samples is needed to elucidate the epigenetic mechanisms of lithium. Finally, the mini review by Rohr and McCarthy [16] discusses the effects of lithium on circadian rhythms. Mechanistic studies in animals and cells and clinical trials in patients affected by bipolar disorder have identified associations between circadian rhythms and the therapeutic effects of lithium. Lithium showed effects on cellular circadian rhythms and increases morningness behaviors in BD patients, changes that may contribute to the therapeutic effects of lithium. However, the authors highlight how much of this evidence is limited by cross-sectional analyses and/or imprecise proxy markers of clinical outcomes and circadian rhythms in BD patients, while mechanistic studies rely on inference from animals or small numbers of patients [16]. As for other molecular mechanisms, further studies are needed to better characterize the longitudinal changes in circadian rhythms in BD patients, and inform the development of therapeutic interventions targeting circadian rhythms.

In sum, this collection of papers offers a perspective on the continuous development of the research on a drug, lithium, that remains fascinatedly obscure in several aspects of its biological actions despite decades of effort dedicated to its comprehension.

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