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REVIEW ARTICLE

Beyond its Psychiatric Use: The Benefits of Low-dose Lithium Supplementation

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Abstract: Lithium is most well-known for its mood-stabilizing effects in the treatment of bipolar disorder. Due to its narrow therapeutic window (0.5-1.2 mM serum concentration), there is a stigma associated with lithium treatment and the adverse effects that can occur at therapeutic doses. However, several studies have indicated that doses of lithium under the predetermined therapeutic dose used in bipolar disorder treatment may have beneficial effects not only in the brain but across the body. Currently, literature shows that low-dose lithium (≤0.5 mM) may be beneficial for cardiovascular, musculoskeletal, metabolic, and cognitive function, as well as inflammatory and antioxidant processes of the aging body. There is also some evidence of low-dose lithium exerting a similar and sometimes synergistic effect on these systems. This review summarizes these findings with a focus on low-dose lithium's potential benefits on the aging process and age-related diseases of these systems, such as cardiovascular disease, osteoporosis, sarcopenia, obesity and type 2 diabetes, Alzheimer's disease, and the chronic low-grade inflammatory state known as inflammaging. Although lithium's actions have been widely studied in the brain, the study of the potential benefits of lithium, particularly at a low dose, is still relatively novel. Therefore, this review aims to provide possible mechanistic insights for future research in this field.

Keywords: Cardiovascular disease, sarcopenia, osteoporosis, obesity, diabetes, Alzheimer's disease, inflammaging, oxidative stress.

1. INTRODUCTION

Lithium (Li) is a monovalent cation, medically known for its mood-stabilizing effects, which have proven extremely useful in the treatment of acute mania and recurring manic episodes and to prevent the risk of suicide in patients with bipolar disorder and schizophrenia [1]. The mechanisms affected by Li treatment in the brain mainly surround its ability to compete with other electrolytes, including sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), and magnesium (Mg^{2+}) [2]. Due to its small ionic radius and monovalent characteristics, Li is able to compete for binding sites with ions of a similar size and conformational arrangement [3]. By competing with these ions, Li can influence the function of ion channels and pumps, ultimately altering brain biochemistry. In addition, Li has been shown to regulate the release of neurotransmitters, such as dopamine, noradrenaline, and serotonin, and has been implicated in the regulation of cyclic adenosine monophosphate (cAMP) and Ca^{2+}-dependent signalling cascades [2, 4], as well as reducing neuronal myoinositol levels and arachidonic acid turnover in neuronal membranes [4]. Many of these mechanisms involve the inhibition of glycogen synthase kinase 3β (GSK3β), inositol monophosphatase (IMPase), and G-protein coupled receptors (GPCRs), which are found throughout different tissues in the body [1, 2]. It is through these collective molecular mechanisms that Li is thought to exert its psychiatric benefits of reducing neuroexcitability and suicidal ideation, although this research is still evolving.

Li carbonate is the most prescribed Li salt, used primarily in the treatment of bipolar disorder. To exert these beneficial effects, Li is administered as an oral tablet at a therapeutic dose of 600-1200 mg/day to ensure it crosses the blood-brain barrier [1]. With such doses, serum Li levels typically range from 0.5-1.2 mM [2]. Unfortunately, these relatively high doses of Li therapy have been associated with adverse effects, which include cardiac arrhythmias and other notable electrocardiographic changes, muscle tremors, weight gain, hypercholesterolemia, hypothyroidism, hyperparathyroidism and hypercalcemia, nephrogenic diabetes insipidus, and renal damage [2, 5]. However, many of these side effects are rare, reversible, and dose-dependent [5]. Importantly, these rare adverse events associated with high dose Li therapy have

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instilled a stigma with Li, leading to an underappreciation of the potential benefits of low-dose Li supplementation.

Sources of dietary Li are largely dependent on the geographical area as some regions, such as Northern Chile, have Li-rich soil, and therefore, have more Li uptake in their water supply, plants, and grains. Research has even suggested that Li may in fact be an essential micronutrient [1, 6]. Studies looking at Li depletion in animal models have shown a marked decrease in fertility and viability of offspring [6], while epidemiological studies in humans have shown that exposure to trace Li in tap water is inversely correlated with hospital admission for mental health, aggressive behaviour, all-cause mortality, suicide mortality, cardiovascular mortality, Alzheimer's disease mortality, and the prevalence of metabolic diseases, such as obesity and diabetes [7-11]. Together, these studies provide the first indication of the possible benefits of low-dose Li on health and longevity. In this review, we will extend beyond these ecological studies and will highlight the current literature focusing on the underlying cellular mechanisms that can contribute to the benefits of low-dose Li consumption. Specifically, we introduce a concept by which low-dose Li may confer cellular resilience against aging by reviewing the effects of Li on various age-related conditions, including cardiovascular disease (CVD), Alzheimer's disease (AD), obesity and diabetes, sarcopenia, osteoporosis, chronic low-grade inflammation, and oxidative stress. For the purpose of this review, low-dose Li will be described as doses that lead to serum concentrations $\leq$ 0.5 mM - the lowest defined therapeutic concentration for bipolar disorder treatment.

2. LOW-DOSE LI AND CARDIOVASCULAR FUNCTION

CVD remains one of the leading causes of death in North America [12, 13], and can be caused by abnormalities of the cardiac muscle, or can occur secondary to pressure or volume overload due to abnormalities of the cardiac or systemic vasculature. These abnormalities put stress on the heart, forcing it to adapt and compensate, which can sometimes lead to maladaptation of the cardiovascular system, resulting in arrhythmias, heart failure, and death [14].

Current literature suggests that therapeutic doses of Li can have adverse effects on the myocardium and myocardial development in patients being treated for bipolar disorder. These effects include T-wave inversions and dysfunction of the sinoatrial (SA) and atrioventricular (AV) nodes leading to arrhythmias [15], concerns over cardiac malformations in the developing fetal heart of pregnant patients [16, 17], and reduced contractile response to adrenergic signalling and atrial fibrosis [18]. However, recent studies have shown that these risks are dose-dependent, with doses often exceeding a serum [Li] of 1.5 mM, and that these risks are much lower than originally thought [2, 17]. Conversely, low-dose Li supplementation may actually provide physiological benefits to cardiac muscle.

2.1. Low-Dose Li may Promote Physiological Hypertrophy

Despite the inability of adult cardiomyocytes to proliferate, the myocardium is still able to adapt to stressors and hormonal changes. This occurs through the process of cardiac hypertrophy, in which adaptations can either be physiological or pathological in nature. Physiological hypertrophy is characterized by normal organization of cardiac structure and normal or even enhanced cardiac function, whereas pathological hypertrophy is commonly associated with upregulation of fetal genes, fibrosis, cardiac dysfunction, and increased mortality [19]. Physiological hypertrophy is stimulated by processes, such as growth and development, pregnancy, and exercise training [20]. However, at other times, a hypertrophic response begins as an acute compensatory and physiological mechanism that aims to increase cardiac output in response to pressure or volume overload, myocardial infarction (MI), arrhythmias, endocrine dysfunction, or genetic disorders [21]. However, chronic hypertrophy of the myocardium caused by these conditions can soon become pathological to the point where the heart can no longer work in a manner sufficient to supply oxygen to the body, let alone meet its own metabolic demands [20].

Interestingly, patients with bipolar disorder are thought to have an increased risk of cardiovascular mortality compared to the general population since cardiovascular and cerebrovascular disorders are the most common cause of death in this patient population [22, 23]. However, in a retrospective review on outpatients attending Li clinics in metropolitan New York City, Prosser and Fieve showed a decreased likelihood of MI with Li treatment at therapeutic doses [23]. Further, in a model of MI in rats, chronic low-dose Li therapy starting 24 hrs post-coronary ligation for 4 weeks at a dose of 1 mmol/kg/day (0.39 mM serum [Li]) led to a reduction of pathological ventricular remodelling post-MI [24]. Li is known to activate insulin-like growth factor 1 (IGF-1), which triggers the phosphoinositide 3-kinase (PI3K)/Akt signalling pathway [25, 26]. In this study, the activation of PI3K *via* Li enhanced protein translation *via* mammalian target of rapamycin (mTOR) signalling; however, at the same time, it also led to improved left ventricular contractility along with reduced fibrotic remodelling, thereby resembling physiological or functional hypertrophy. Indeed, the activation of the p110α PI3K isoform by Li has also been shown to promote physiological hypertrophy over pathological remodelling [24].

Activation of the PI3K/Akt pathway also regulates GSK3 activity, a well-known serine/threonine kinase that is involved in a wide range of signalling pathways in the body [27]. Li inhibits GSK3 both directly by competing with its cofactor of activation Mg^{2+} and indirectly by activating PI3K/Akt, which phosphorylates and inhibits GSK3 (Ser21 on GSK3α and Ser9 on GSK3β isoforms, respectively) [28, 29]. GSK3β is the dominant isoform found in the heart and is constitutively active to prevent hypertrophy of the heart under normal conditions [30]. Though in pathological conditions, GSK3β signalling can also become maladaptive [31].

One of the many functions of GSK3β is the ability to bind to the promoter of the *ATP2a2* gene and prevent the transcription of the sarco(endo)plasmic reticulum Ca^{2+} - ATPase (SERCA). SERCA is a Ca^{2+} handling protein found in the membrane of the sarcoplasmic reticulum (SR) and is responsible for moving Ca^{2+} from the cytosol to be stored in the SR, essentially regulating cardiac muscle relaxation and muscle contraction in an indirect manner through regulating

SR Ca^{2+} store. The importance of SERCA was made evident with a previous study showing that cardiac overexpression of the dominant cardiac isoform, SERCA2a, increases cardiac contractile function [32]. Moreover, a recent work from our lab shows that treating male C57Bl/6J mice with a sub-therapeutic dose of Li (10 mg/kg/day for 6 weeks leading to a 0.02 mM serum [Li]) leads to cardiac GSK3 inhibition, increased expression of SERCA2a, and improvements in SERCA activity [11], which ultimately enhance stroke volume and cardiac output. Despite its role in preventing cardiac hypertrophy, inhibiting GSK3 did not lead to any alterations in cardiac muscle size or histology, suggesting that with this dose of Li, only cardiac muscle function was improved [12]. In this same study, we also found a significant decrease in the expression of SERCA regulator phospholamban (PLN), which acts as an inhibitor of SERCA by binding to the SERCA pump and reducing its affinity for Ca^{2+} [11]. To our knowledge, GSK3 itself does not regulate PLN expression in the same way in which it regulates SERCA2a. Therefore, we speculate that this effect of Li in lowering PLN could be occurring *via* a GSK3-independent pathway [33]. In this respect, Li has been shown to activate autophagy through its regulation of IMPase [34]. A work by Teng *et al.* has shown that PLN can be targeted by autophagic degradation in cultured mouse neonatal cardiomyocytes (CMNCs) [35]. Therefore, it is possible that Li treatment could induce autophagic degradation of PLN, but this requires further investigation. Nevertheless, the reduction in PLN and increase in SERCA with Li treatment increase the ratio of the Ca^{2+} pump relative to its inhibitor PLN, which could lead to improvements in SERCA and cardiac function.

While promising, it is important to acknowledge the concern that chronic inhibition of GSK3 in the heart may contribute to hypertrophy [36]. For example, Tateishi *et al.* have shown the inhibition of GSK3 with 20 mg/kg/day Li to have an additive effect on cardiac hypertrophy in aortic banding in rats (a model of pressure overload hypertrophy) [37]. Specifically, cardiac weight was significantly increased post-surgical intervention along with significant increases in thickness of the posterior wall and interventricular septum [37]. However, whether these changes were associated with impairments in contractility (*i.e.*, stroke volume, fractional shortening, *etc.*) was not specifically examined in this study, and thus, we are unable to determine whether the additive effect of Li resulted in pathological or functional hypertrophy. Future studies could examine the effect of Li on cardiac contractility and SERCA function in the aortic banding model.

2.2. Low-Dose Li and Vascular Function

The maintenance of healthy vasculature is important for maintaining cardiac and overall health. Vascular dysfunction can contribute to the development and progression of pathologies by altering blood flow and pressure, leading to reduced oxygen delivery and metabolite transport to and from various organs, respectively, as well as increasing the workload of the heart, contributing to the development of cardiomyopathies and eventual heart failure [38]. Vascular dysfunction can occur due to injury to the endothelial layer within blood vessels, often seen in atherosclerosis, and can occur naturally as we age, causing impairments in endothelium-dependent vasodilation [39]. The development of atherosclerosis and impairments in endothelial function are significant contributors to the development of age-related CVD, and therefore, preserving endothelial function and preventing the formation and build-up of atherosclerotic plaque are important therapeutic targets for maintaining vascular health [38, 40].

In the late 1960s, an ecological study by Voors showed a correlation between tap water hardness and risk of atherosclerotic heart disease (AHD), specifically showing higher prevalence in cities lacking Li in their tap water [41]. In 1970, Voors showed correlations between six elements (calcium, chromium, lithium, magnesium, vanadium, and zinc) in drinking water that had suspected effects on AHD risk and their correlations with AHD mortality of caucasian inhabitants across 100 U.S. cities. Among these elements, Li had the strongest negative correlation with AHD mortality and the highest proportion of human absorption from drinking water compared to the other 5 elements [42]. Since this time, work has been done to determine a more causal relationship between lithium's effects on the body and atherosclerotic risk.

In the development of atherosclerosis, endothelial injury induces the expression of adhesion molecules that recruit T cells and monocytes locally. Monocytes differentiate into macrophages and begin to consume lipids, becoming foam cells that lie within the vascular intima. Foam cells accumulate in the intima and form atherosclerotic plaques producing inflammatory mediators, which increase the risk of further endothelial injury and plaque formation [43]. Left unchecked, a build-up of plaque narrows the vasculature, increasing total peripheral resistance, which the heart must work against. A study by Choi *et al.* investigated the effects of low-dose (10 mg/kg/day) LiCl treatment in a model of atherosclerosis induced by high-fat feeding in the ApoE-deficient ($ApoE^{-/-}$) mouse, a model lacking the cholesterol metabolic regulator apolipoprotein E (APOE). In high-fat diet-fed (HFD) mice given LiCl for 6- and 14 weeks, there was a significant decrease in blood glucose levels and atherosclerotic lesions in the aorta and aortic valve compared to HFD alone in $ApoE^{-/-}$ mice. From a mechanistic perspective, LiCl treatment also decreased vascular adhesion molecule-1 (VCAM-1) expression, allowing for a reduction in monocyte binding to the endothelial wall, preventing the accumulation of macrophages in the intima [43]. In addition, GSK3 activity has been suggested to increase levels of free fatty acids (FFA), potentially leading to increased low-density lipoprotein (LDL), which contributes to the formation of foam cells [44]. Choi *et al.* showed no differences in plasma FFA or high-density lipoprotein (HDL); however, they did observe a reduction in plasma total cholesterol in the 14-week LiCl+HFD conditions compared to HFD alone, suggesting a potential decrease in plasma LDL levels with LiCl treatment. The potential effects of LiCl and GSK3 on lipid profile should be examined more closely to further understand their possible protective effects in atherosclerotic development [43].

Endothelial function is another important factor in vascular health that is impacted by aging. Specifically, the endothelium, which makes up the inner lining of the arteries, maintains vascular tone, prevents adhesion of platelets and

inflammatory cells, promotes the breakdown of fibrin, and limits vascular proliferation. When these functions are impaired, endothelial dysfunction can contribute to atherosclerosis, increase blood pressure, tissue ischemia, and infarction [38]. Perhaps the best-known role of the endothelium is to promote vasodilation by secreting nitric oxide (NO) that causes the neighbouring smooth muscle cells to relax. As we age, however, there is reduced NO bioavailability as a result of elevated oxidative stress, impairing endothelium-dependent vasodilation, which ultimately increases blood pressure and total peripheral resistance [45]. Together, these factors can cause stress on the myocardium leading to pathological remodelling of the heart, further increasing the risk of developing cardiomyopathies and progression to heart failure [20].

Throughout the literature, there have been conflicting results related to the effects of Li on vasodilation [46-49]. In 2007, Afsharimani *et al.* conducted a chronic LiCl treatment in rats giving them 600 mg/L LiCl for 30 days resulting in a 0.3 mM serum Li concentration. This treatment was shown to increase endothelium-dependent vasorelaxation in arteries of the mesenteric vascular bed. The mechanism behind this action was suggested to be through the inhibitory effect of Li on IMPase, which reduces the production of inositol-3,4,5-phosphate (IP3) and decreases Ca^{2+} release from the endoplasmic reticulum (ER). This inhibition reduces intracellular free Ca^{2+} concentrations, resulting in less cellular stress due to Ca^{2+} overload in the cytosol [47]. However, not much later, Rofouyi *et al.* found that isolated rat mesenteric arteries pre-treated with Li (0.5 and 1.0 mM LiCl) had inhibited endothelium-dependent vasodilation, and could only observe improvements in endothelium-dependent vasodilation with supra-therapeutic doses of Li (2 and 2.5 mM LiCl) [48]. In this work, the authors suggested that the decrease in intracellular Ca^{2+} may actually limit NO bioavailability, which is plausible since nitric oxide synthase (NOS) is a Ca^{2+}/calmodulin dependent enzyme [50]. However, later in 2016, Bosche *et al.* published two papers investigating varying concentrations of LiCl pre-treatment of isolated arteries [46, 49]. The first used concentrations varied from 0.4 mM (low dose) to 100 mM (supra-therapeutic dose) in mouse aorta and pig middle cerebral arteries. In these experiments, the authors observed the opposite effect of increasing Li concentrations compared to the results of Rofouyi *et al.*, since 0.4 mM LiCl slightly improved endothelium-dependent vasodilation, whereas increasing the concentrations to 0.8 mM and 100 mM progressively decreased endothelium-dependent vasodilation [49]. Mechanistically, Bosche *et al.* suggested that such high concentrations of Li cause too much inhibition of IMPase and, like Rofouyi *et al.* suggested, the resulting decrease in Ca^{2+} lowers NO availability, and therefore, vasorelaxation [17]. Their second paper then looked at a sub-therapeutic range of 0.2-0.4 mM LiCl in isolated mouse aorta and pig middle cerebral arteries. Interestingly, within this sub-therapeutic range of LiCl, the authors found a dose-dependent increase in endothelium-dependent vasorelaxation in cerebral and vascular arteries [46].

Despite these discrepancies, one thing that appears to be clear is that Li (at any concentration) has no effect on the relaxation of vascular smooth muscle cells independent of the endothelium [46-49]. However, more research is needed to investigate the mechanism behind the dose-dependent effects of Li on endothelium-dependent vasorelaxation. Future studies should focus on the long-term treatment of Li (at varying doses) in *in vivo* models for a better understanding of its potential therapeutic mechanisms in physiologically relevant conditions.

2.3. Summarizing the Impact of Li on Cardiovascular System

Low doses of Li, mainly in the form of LiCl salt, have an effect not only on myocardial function and adaptation, but also on vascular health. By activating PI3K/Akt signalling pathways, low-dose Li has the potential to increase cardiac contractile function by inhibiting GSK3 and promoting SERCA2a expression while potentially promoting cell survival by inducing autophagy through inhibition of IMPase. The inhibition of GSK3 and IMPase seen with low-dose Li treatment in the vasculature has also been shown to affect endothelium-dependent vasorelaxation while also preventing macrophage infiltration and foam cell formation, ultimately leading to reduced stiffening and occlusion of arteries caused by vascular injury and dysfunction (Fig. **1**). By producing these effects, low-dose Li has the strong potential to provide cellular resilience against cardiovascular aging; however, this warrants future investigations.

3. LOW-DOSE LI AND MUSCULOSKELETAL HEALTH

Functional decline of the musculoskeletal system occurs inevitably with aging, often in the form of sarcopenia and osteoporosis [51]. Osteoporosis is characterized by low bone mineral density (BMD), deterioration of bone mineralization, and decreased bone strength, leading to increased risk of fractures [52]. Osteoporosis is also more likely to occur in post-menopausal women compared to aging men due to the loss of estrogen, which has anti-inflammatory and Ca^{2+} regulatory functions [53]. Specifically, both women and men naturally begin losing bone in the third decade of life at a rate of 0.5-1 % per year, but around menopause, women start losing bone at an accelerated rate of 2-3 % per year. Men lose bone more slowly as they age, with a higher rate of bone loss after about the age of 65 [54, 55]. Similarly, age-related sarcopenia is a combined decline in muscle mass and strength starting at the age of 50. From this age, muscle mass decreases at a rate of 1-2% per year, and muscle strength starts declining by 1.5% per year and accelerates to 3% per year after the age of 60 [56, 57]. Sarcopenia is associated with other health implications involving metabolism and immunity; however, reduced mobility and disability are the most critical risk factors for sarcopenia [57]. Importantly, changes in muscle mass and strength are also associated with the changes in bone health and development, where declines in muscle strength and mass have been associated with increased risk of fragility fractures and lower BMD [58].

3.1. Low-Dose Li and Osteoporosis

There is some speculation in the literature suggesting that chronic Li treatment in patients with bipolar disorder increases the risk of osteoporosis and bone turnover by

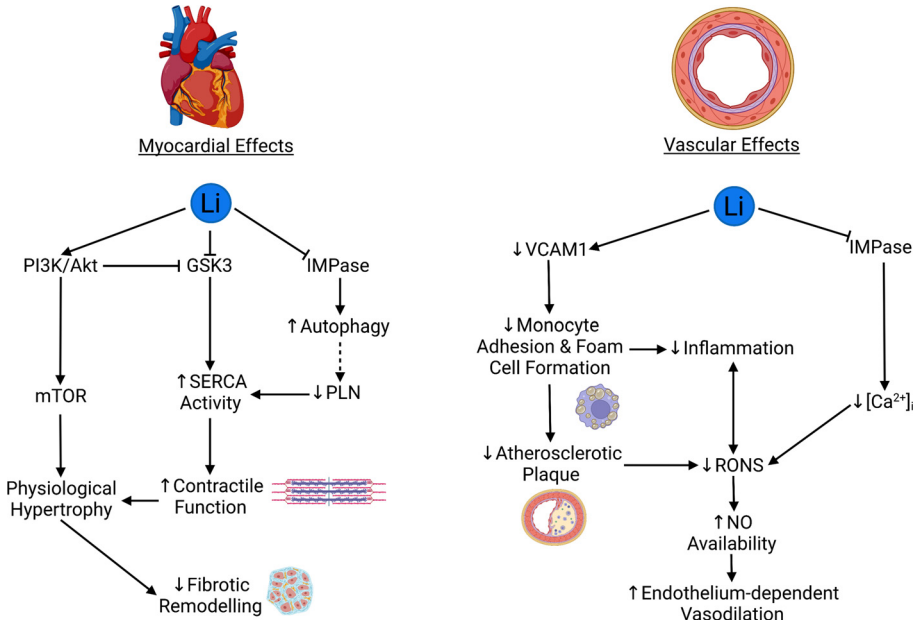

Fig. (1). Low-dose lithium affects myocardial and vascular endothelial function. In the myocardium (left panel), low-dose Li has been shown to activate the PI3K/Akt signalling pathway to promote physiological hypertrophy by increasing mTOR signalling and inhibiting GSK3 activity. Low-dose Li can also inhibit GSK3 directly, which allows for increased function of the SERCA pump, potentially enhancing contractile function. Li can also inhibit IMPase, increasing autophagy and potentially reducing the expression of SERCA inhibitor PLN. In the vasculature (right panel), low-dose Li reduces expression of VCAM1, leading to reduced atherosclerotic plaque formation and its associated inflammation. The inhibition of IMPase by Li also regulates intracellular calcium ($[Ca^{2+}]_i$) levels, reducing reactive oxygen/nitrogen species (RONS) and increasing availability of nitric oxide (NO) to increase endothelium-dependent vasodilation. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

increasing parathyroid hormone (PTH) levels, which increase serum Ca^{2+} concentration *via* bone excretion [59, 60]. However, given its well-known effect on GSK3 activity, Li therapy has also been shown to promote bone formation, with varying effects on bone resorption [61]. Indeed, although more research is needed to investigate the effects of differing doses, compounds and durations of Li treatment on bone health, the current literature suggests that when consumed in low doses, Li may have a positive effect on bone structure and function [60].

In a recent study, we found that young (3-6 months old) male C57BL/6J mice fed a low dose of LiCl (10 mg/kg/day of LiCl over a 6 weeks period and serum [Li] of 0.02 mM) exhibited significant inhibition of GSK3 in the femur [62]. GSK3 is a negative regulator of the Wnt signalling pathway, a well-known anabolic pathway in bone [63]. When Wnt ligands are present and bind to the Frizzled (FZD) receptor and co-receptors LRP5 or LRP6, Wnt signalling is "turned on" [64]. The active FZD receptor stimulates disheveled protein, which prevents the formation of the destruction complex made up of GSK3β, APC and axin. Within this complex, GSK3β phosphorylates β-catenin, marking it for proteolytic degradation. However, upon Wnt activation, GSK3β is unable to phosphorylate β-catenin, allowing for β-catenin to accumulate and translocate into the nucleus, where it stimulates translation of Wnt target genes, such as alkaline phosphatase, Runx-2, and osterix, promoting the proliferation and differentiation of osteoblasts and the production of osteoprotegerin (OPG) [64, 65]. OPG is secreted by osteoblasts and acts as a decoy-receptor for receptor activator of nuclear factor-κB ligand (RANKL), preventing the formation, proliferation, and activation of osteoclasts (bone-resorbing cells) [61, 65]. In our previous study, and along with GSK3 inhibition in the femur, we also observed a significant increase in OPG expression with no change in RANKL, ultimately leading to an increase in bone formation by sub-therapeutic Li supplementation in healthy young male mice [62].

In a genetic model of osteoporosis, *Lrp5* knockout (*Lrp5*$^{-/-}$) mice, low-dose Li treatment also enhanced bone formation [66]. These mice lack the LRP5 co-receptor, leading to impairments in Wnt activation and thus declines in bone mass and BMD and enhanced skeletal fragility. Clément-Lacroix *et al.* investigated the effects of a daily 4-week low-dose Li treatment (200 mg/kg/day *via* oral gavage, 0.4 mM serum [Li]). As Li can inhibit GSK3 in the absence of Wnt activation *via* Mg^{2+} competition and Ser9 phosphorylation, Li was able to bypass the defect in Wnt signalling. In the end, this resulted in an increase in bone formation rate, trabecular number, bone volume fraction, and the number of osteoblasts, ultimately leading to a bone mass that was restored to near wild-type (WT) levels [66]. In another model of osteoporosis induced by ovariectomy, 2 weeks of low-dose Li treatment (20 mg/kg/day estimated serum [Li] = 0.35-0.37 mM) enhanced fracture healing when Li treatment started at 7 or 10 days post-femoral-fracture [67]. When measured at 4 and 6 weeks post-fracture, biomechanical testing of the femur revealed that rats treated with Li, again for only 2 weeks, had increased maximum torque [67]. The authors suggest that the improved effect of Li treatment is a result of taking advantage of naturally increased Wnt signalling in the healing process, where the Li treatment provides additional

Wnt activation and GSK3 inhibition, thereby speeding up osteoporotic fracture healing [67, 68]. Together, these studies show that low-dose Li may act to prevent or slow the progression of bone loss and may also improve the outcome after an osteoporotic fracture.

3.2. Low-Dose Li and Sarcopenia

Sarcopenia is described as an age-related decline in muscle mass and strength. It is thought to be caused by a reduction in physical activity and mobility, malnutrition, low protein intake, changes in hormones and metabolism, systemic inflammation, and a loss of motor neurons due to neuromuscular aging [69]. GSK3 is a well-established negative regulator of muscle mass that inhibits protein synthesis and promotes protein breakdown [70, 71], and has recently been suggested to be a potential therapeutic target for conditions of muscle disuse atrophy, including age-related sarcopenia [72]. Recent work from our lab has shown that low-dose Li (0.5 mM) augments myoblast fusion and myogenic differentiation in C2C12 cells by activating the Wnt signalling pathway [73]. Myoblast fusion is a critical component of the muscle regenerative process, whereby after an injury, muscle stem cells (satellite cells) are activated to differentiate and repair damaged muscle. This is important as diminished myogenic differentiation and fusion capacity are thought to contribute to age-related muscle loss [74]. While our study is not the first to showcase the myoblast fusion augmenting effect of Li, it is important to note that most studies have utilized supraphysiological levels of Li exceeding 1 mM in concentration [75-78].

In vivo and with a much smaller dose of Li (10 mg/kg/day for 6 weeks; serum [Li] = 0.02 mM), we have also recently shown that supplementation increases muscle strength and fatigue resistance in young (3-6 month old) male mice [79]. Specifically, we found that low-dose Li increased force-producing capacity in the soleus and extensor digitorum longus. The exact mechanisms leading to the increased muscle strength with Li supplementation remain unknown, but we suspect that its effect on myoblast fusion could enhance muscle quality. In addition, we also found that Li supplementation enhanced fatigue resistance in the soleus muscle [79]. This result was associated with an increase in slow-oxidative fibres. Generally speaking, muscle is comprised of slow-oxidative and fast-glycolytic fibres that differ in metabolic machinery and contractile characteristics (*i.e.*, force produced and kinetics) [80]. In the context of aging, where sarcopenia primarily affects the fast-glycolytic fibres [56], promotion of the oxidative fibres with Li supplementation could be seen as beneficial. This shift towards the oxidative fibre type occurs due to the inhibition of GSK3 that was observed with Li [79]. In the muscle cell, GSK3 antagonizes the oxidative fibre type by inhibiting calcineurin signalling and the nuclear localization of nuclear factor of activated T-cells (NFAT) [72]. Interestingly, a recent study found naturally occurring (*i.e.*, without supplementation) plasma Li levels to be positively correlated with endurance exercise performance in sixty-five high-level middle and long-distance runners [81], which appears to support our previous findings in the rodent model. Whether this is due to differences in fibre type composition should be investigated in future studies. Altogether, low-dose Li supplementation could potentially combat age-related declines in muscle mass and strength; but this should be specifically tested in both male and female aged mice and/or humans to also determine if biological sex may have an effect.

3.3. Effects of Exercise and Li on Muscle and Bone

In both conditions of sarcopenia and osteoporosis, aerobic and resistance training are recommended to try to maintain muscle and bone strength and prevent further wastage of these tissues [82, 83]. Exercise induces mechanical signals for cytoskeletal and transmembrane-bound proteins, such as integrins, which elicit increased Wnt/β-catenin signaling in the bone, promoting bone formation and suppressing bone resorption. These signals also affect mesenchymal stem cell differentiation into osteoblasts [84]. Mechanical stimulation by different types of exercise also inhibits the expression of the GSK3 activator, sclerostin. Sclerostin is an osteokine secreted by the osteocytes in response to mechanical unloading, which, when active, binds to LRP5 and LRP6 to prevent binding of the Wnt ligand and subsequent Wnt signalling and GSK3 inhibition. Thus, sclerostin expression is increased during periods of immobilization, contributing to increased GSK3 activity seen with functional musculoskeletal decline [85]. In muscle, aerobic exercise increases oxidative capacity, which increases the resistance to fatigue by increasing mitochondrial biogenesis through the promotion of peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC-1α) expression. Conversely, resistance training in muscle produces anabolic effects through increased mTOR signalling, allowing for increased muscle protein synthesis [86]. IGF-1 is also produced by muscle through mechanotransduction and contributes to muscle protein synthesis and anti-catabolic pathways [87].

To our knowledge, there have been no published studies looking at a combined effect of Li, at any dose, and exercise on muscle or bone structure and strength. However, a recent study from our lab examined the association between changes in serum Li and changes in total muscle strength and markers of bone turnover in university-aged males who have undergone 12 weeks of resistance exercise training while supplementing with Greek yogurt [88, 89]. Interestingly, we found that serum Li decreases with exercise training, potentially by being secreted through sweat. However, serum Li levels were maintained with exercise when Greek yogurt was consumed 3 times a day on training days and 2 times a day on non-training days. We presume that this is due to the fact that dairy products, such as yogurt, can act as a dietary source of Li, with Greek yogurt containing 0.07 ± 0.04 mg/kg of Li [90]. Furthermore, we found maintaining serum Li levels with resistance training to be positively associated with greater gains in total muscle strength and markers of bone turnover [91]. Specifically, we found changes in serum Li to bepositively associated with the P1NP:CTX ratio, which provides a marker for bone formation over bone resorption. P1NP is procollagen type 1 N-terminal propeptide and CTX is β-isomerized carboxy-terminal cross-linking telopeptides, and both are commonly used markers for bone formation and turnover, respectively, which are also recommended for clinical use by the International Osteoporosis Foundation [92]. As dairy products, such as Greek yogurt, also contain calcium, protein, phosphorus, and potassium

that may also impact musculoskeletal health, we also controlled for these additional components in our analyses. As expected, correlations between serum Li and total strength and the P1NP:CTX ratio were found to be weakened after controlling for these factors [91]. Nevertheless, our recent findings suggest that dietary Li in Greek yogurt may be an additional component that contributes to muscle and bone anabolism, so future studies should examine the effects of dietary Li and exercise in young and old men and women.

3.4. Summarizing the Impact of Li on the Musculoskeletal System

As our population continues to age, the functional decline of the musculoskeletal system also continues to increase. Although many medications used in the treatment of osteoporosis focus on preventing resorption, low-dose Li may have potential effects in promoting bone formation and/or suppressing bone resorption and improving fracture healing mainly through its direct and indirect inhibition of GSK3β and its subsequent effects on Wnt/β-catenin signalling. This same mechanism of GSK3 inhibition may also help maintain skeletal muscle function through improvements in calcineurin signalling, which could prove useful in both the treatment of sarcopenia and in the maintenance of bone strength and structural integrity (Fig. **2**). With regular exercise as a common prescription for the treatment and prevention of functional musculoskeletal decline, it has been postulated that the addition of low-dose Li treatment could enhance the anabolic effect of exercise on these systems. Although there is limited work in this area, there is promising correlational data between combined exercise and low-dose Li supplementation in human subjects that warrant further investigation.

4. LOW-DOSE LI AND OBESITY AND DIABETES

The prevalence of obesity and type 2 diabetes mellitus (T2DM) continues to rise at an alarming rate. Aging plays a critical role in the development of these metabolic disorders, and there is a growing concern related to them from health and economic standpoints as the global population continues to age [93, 94]. Obesity is defined as a body mass index (BMI) of 30 kg/m^2 and is caused by a positive energy imbalance, where the amount of calories consumed far exceeds the amount of calories expended, leading to excessive accumulation of fat that could negatively impact health and quality of life [94]. This accumulation of fat tissue puts individuals at a substantially higher risk for developing insulin resistance and progression to T2DM [95]. T2DM occurs when cells of the skeletal muscle, liver, and adipose tissues have a reduced response to insulin and can arise from several different factors, including reduced physical activity, poor diet, aging, and/or genetics. The reduced response or resistance to insulin causes the β-cells of the pancreas to work harder to produce more insulin and to try to make up for the lack of response from the peripheral tissues [96]. However, this causes chronic stress on the β-cells eventually leading to reduced secretion of insulin and subsequent hyperglycemia [95, 96]. Together, both obesity and T2DM increase the risk of developing many other serious conditions, such as cardiovascular diseases, reduced pulmonary function, systemic inflammation, neurocognitive decline, and increased stress on joints [93, 94]. As such, current research efforts have heavily focused on the discovery of novel therapeutic agents and strategies aimed at combating these metabolic disorders. Of interest, we have recently shown, at the population level, trace levels of Li found in publicly available drinking water to be negatively associated with the prevalence of obesity and diabetes across the state of Texas [8].

4.1. Low-Dose Li and Obesity

Li therapy has been associated with increased weight gain in patients with bipolar disorder; however, it is uncertain if Li itself is the actual cause of weight gain in this patient population [97]. It is important to note that not all patients taking Li experience weight gain, and those with bipolar disorder are already at risk of obesity, independent of any medication [98]. Moreover, recent studies in rodent models have shown that low-dose Li supplementation, with levels well below those used for bipolar disorder, may attenuate diet-induced obesity. In the study by Choi *et al.*, 14-week treatment of HFD-fed ApoE-deficient mice with 10 mg/kg/day LiCl led to significantly attenuated weight gain compared to untreated HFD-fed ApoE-deficient mice [43]. Recently, using the same dose, Jung *et al.* found that LiCl treatment for 12 weeks blunted HFD-induced weight gain in male Sprague Dawley rats, an effect similar to that seen with exercise training [99].

In our lab, we recently treated both chow-fed and HFD-fed male C57BL/6J mice with 10 mg/kg/day for 6 (chow) or 12 (HFD) weeks (Geromella *et al.*). Though we did not see any differences in body mass or fat composition, we did find that LiCl-treated mice consumed more calories throughout the treatment protocol. This effect is consistent with the mechanisms thought to contribute to the increased risk for developing obesity with high-dose Li therapy; however, the increase in caloric consumption did not accord with an increase in body mass. In fact, after calculating the metabolic efficiency or the body mass gained per kCal consumed [100], we found that Li treatment reduced metabolic efficiency under chow and HFD-fed conditions (Ryan *et al.*). This result was associated with elevations in total daily energy expenditure, which we attribute to an effect of Li on stimulating adaptive thermogenic mechanisms.

Adaptive thermogenesis is the process by which chemical energy is dissipated as heat in response to prolonged cold exposure or caloric excess, leading to enhanced combustion of metabolic substrates (*i.e.*, fatty acids and glucose) [101]. Since obesity is a result of an energy surfeit, promoting adaptive thermogenesis and energy expenditure may be useful in fighting off excessive adiposity [102]. In mammals, there are two primary sites for adaptive thermogenesis: 1) skeletal muscle and 2) brown/beige adipose tissue [103, 104]. In skeletal muscle, SERCA-mediated Ca^{2+} cycling is the primary mechanism for adaptive thermogenesis [102-104]. Under optimal conditions, SERCA has a 2:1 coupling ratio, which suggests that SERCA transports 2 Ca^{2+} ions into the SR for every 1 ATP hydrolyzed. However, SERCA-mediated Ca^{2+} transport can be uncoupled by ATP hydrolysis *via* interaction with sarcolipin (SLN) [105-109] or neuronatin (NNAT) [110], thereby increasing the energetic cost of the SERCA pump in muscle. In brown and beige adipose tissue, uncoupling protein 1 (UCP1) uncouples mitochondrial proton-motive force from ATP synthesis, providing a fu-

tile energetic cycle that drives the combustion of metabolic fuels [111]. Beige adipocytes are of particular importance in the context of obesity, since they are thought to be a distinct type of adipocyte found within white adipose tissues (fat-storing cells), which when activated, become a more brown-like cell. Since obesity is characterized by an abundance of white adipose tissue, activating these cells' sensitivity to the beiging process would be advantageous. In our recent work, we found that the elevated energy expenditure and lowered metabolic efficiency seen with Li supplementation in chow- and HFD-fed mice were caused by an increase in either SERCA uncoupling or white adipocyte 'beiging' (Geromella *et al.*). Future studies from our lab will determine whether low-dose Li can prevent HFD-induced obesity under pair-fed conditions and whether biological sex can influence the effect of Li on energy homeostasis, as most studies to date have solely used male rodents.

4.2. Low-Dose Li and T2DM

T2DM most commonly occurs when blood glucose levels are chronically elevated to the point where not enough insulin can be produced by the pancreas to remove it from the blood and store it in tissues [112]. When blood glucose levels rise, insulin is secreted by the pancreas and binds to insulin receptors in the liver, skeletal muscle, and fat cells to elicit glucose uptake and clearance from circulation. For example, in muscle, the binding of insulin to its receptor leads to a sequence of events that cause the translocation of vesicles containing glucose transporters (GLUT4) to the cell membrane [113], allowing for glucose entry into the cell where it can be stored as glycogen or utilized to produce ATP [112]. However, in T2DM, insulin-sensitive tissues, such as skeletal muscle, become non-responsive to insulin, eventually leading to β-cell exhaustion and a reduction in insulin levels.

Since the 1960s, Li has been known to exert insulin-mimetic effects [114-116], improving glucose homeostasis in patients taking Li as medication [117-119]. Conversely, discontinuation of Li therapy in patients with bipolar disorder has been associated with transient diabetes [120], which altogether showcases the effect of Li on improving glucose homeostasis. The benefits of Li on glucose homeostasis have been attributed to the inhibition of GSK3 and subsequent increase in muscle glycogen production, the enhancement of the insulin signaling cascade, GLUT4 translocation, as well as its effects on IP3 metabolism and intracellular Ca^{2+} levels [99, 114, 121, 122]. With respect to low-dose Li supplementation, Choi *et al.* found plasma glucose levels to be significantly decreased in ApoE-deficient mice fed an HFD along with LiCl (10 mg/kg/day) compared to untreated HFD-fed ApoE-deficient mice with both 6 and 14 weeks of treatment [43]. Moreover, Jung *et al.* found that 12 weeks of Li treatment (10 mg/kg/day) lowered blood glucose and insulin levels in HFD-fed male Sprague Dawley rats to levels similar to that of chow-fed controls [99]. Strikingly, this effect of Li treatment was similar to that observed with exercise and high-fat feeding, suggesting that at least to some extent, Li may provide similar benefits to metabolic health as regular exercise. We recently raised this point in a previous study, where low-dose Li supplementation inhibited GSK3 in the soleus, leading to enhanced fatigue resistance, as regular exercise is also known to enhance muscle performance [123]. Collectively, the current literature suggests that low doses of Li may still produce the insulin-mimetic effects in rodents, where it can offset the deleterious effects of an HFD on glucose regulation. Future studies should examine the importance of biological sex and should attempt to extend these findings to the human population.

4.3. Low-Dose Li and Type 1 Diabetes

While the present review focuses on the role of low-dose Li in age-related conditions, such as obesity and T2DM, it is important to acknowledge the literature that also suggests that Li may benefit those living with type 1 diabetes (T1D). T1D is known as insulin-dependent diabetes and is a chronic condition where the pancreas is unable to produce sufficient amounts of insulin. In the streptozotocin (STZ)-induced murine model of T1D, acute microdose (40 mg/kg single-day injection) Li therapy improved hyperglycemia, attenuated body weight loss and signs of diabetic kidney injury [124]. Mechanistically, this effect was due to the inhibition of GSK3, which protected the pancreatic cells against oxidative stress. This pancreatic protective effect was also observed in STZ mice treated with either LiCl or Li carbonate for 28 days (10 and 8.9 mg/kg/day, respectively), where Li treatment attenuated hyperglycemia, weight loss and polydipsia [125]. Finally, Jung *et al.* also found that low-dose Li treatment improved insulin-mediated glucose removal in the STZ-induced mouse model of T1D [81, 99].

4.4. Summary of the Effects of Li on Metabolic Health

Although Li has been thought to be associated with weight gain in patients with bipolar disorders, our findings show that low-dose Li in various models appears to have beneficial effects on energy and fat metabolism, which could potentially have therapeutic implications for the treatment of obesity and T2DM (Fig. **3**). In fact, GSK3 inhibition *via* low-dose Li may provide antioxidant effects that protect pancreatic cells from damage, and therefore, along with its well-known insulin-mimetic effects, may also prove to be beneficial in the treatment of T1D (Fig. **3**). So far, very few studies have looked at low doses of Li treatment *in vivo*, and there are still discrepancies in how effective these doses are in regulating glucose metabolism. Therefore, we can only speculate that consistent treatment over a period of time in animal models may elicit similar effects as those shown above and that perhaps combining exercise and insulin treatment with low-dose Li may have synergistic effects in combatting obesity and obesity-induced insulin resistance and hyperglycemia.

5. LOW-DOSE LITHIUM AND ALZHEIMER'S DISEASE

Cognitive decline is a naturally occurring aspect of aging, normally starting after the age of 65. However, the prevalence of dementia, which is defined as the development of cognitive deficits that interfere with activities of daily living, also increases with age, doubling every 5-6 years after the age of 65 [126]. Alzheimer's disease (AD) is estimated to make up about 60-80% of dementia cases and presents clinically as cognitive dysfunction, loss of memory, and changes in personality. It can develop early in life due to familial genetic predisposition, known as familial AD [127], or it can

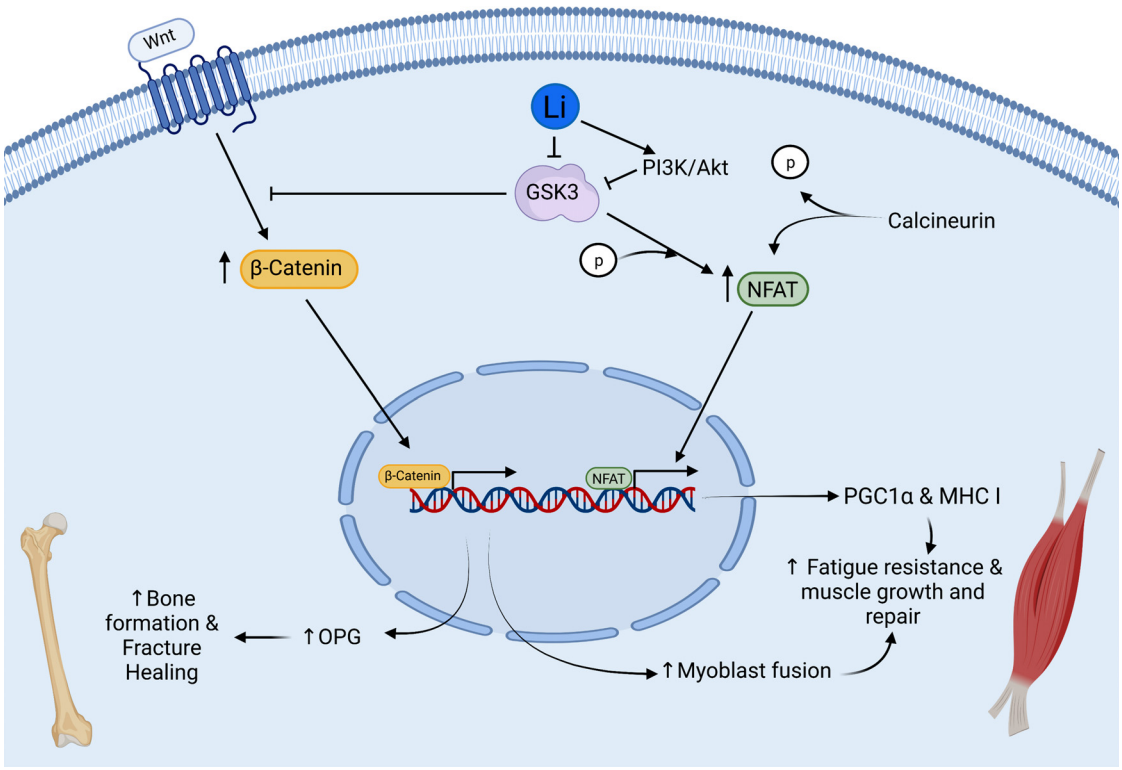

Fig. (2). Potential benefits of low-dose lithium in bone and muscle. Low-dose Li directly and indirectly inhibits GSK3 activity to allow for Wnt signalling in bone and muscle, which promotes accumulation and translocation of β-catenin into the nucleus. Transcription of Wnt target genes increases the expression of osteoprotegerin in the bone to promote bone formation during growth and healing. Wnt signalling also promotes transcription of myogenic regulatory factors, which promote muscle growth and repair. The inhibition of GSK3 also enhances calcineurin signalling and the dephosphorylation of NFAT, which allows for its nuclear translocation and transcription of slow oxidative genes, ultimately promoting fatigue resistance in skeletal muscle. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

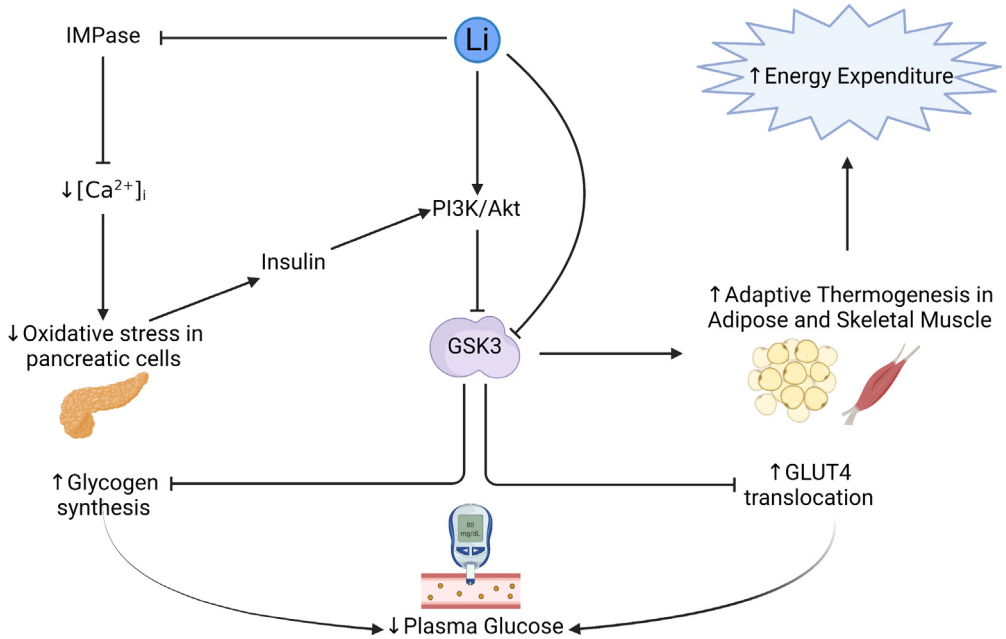

Fig. (3). Effects of low-dose lithium on glucose regulation, energy expenditure, and the pancreas. Low-dose Li reduces plasma glucose levels and increases adaptive thermogenesis in skeletal muscle and adipose through its inhibition of GSK3 activity. By inhibiting IMPase, low-dose Li reduces intracellular calcium levels ($[Ca^{2+}]_i$), relieving oxidative stress in pancreatic cells allowing for insulin production, and further, GSK3 inhibition. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

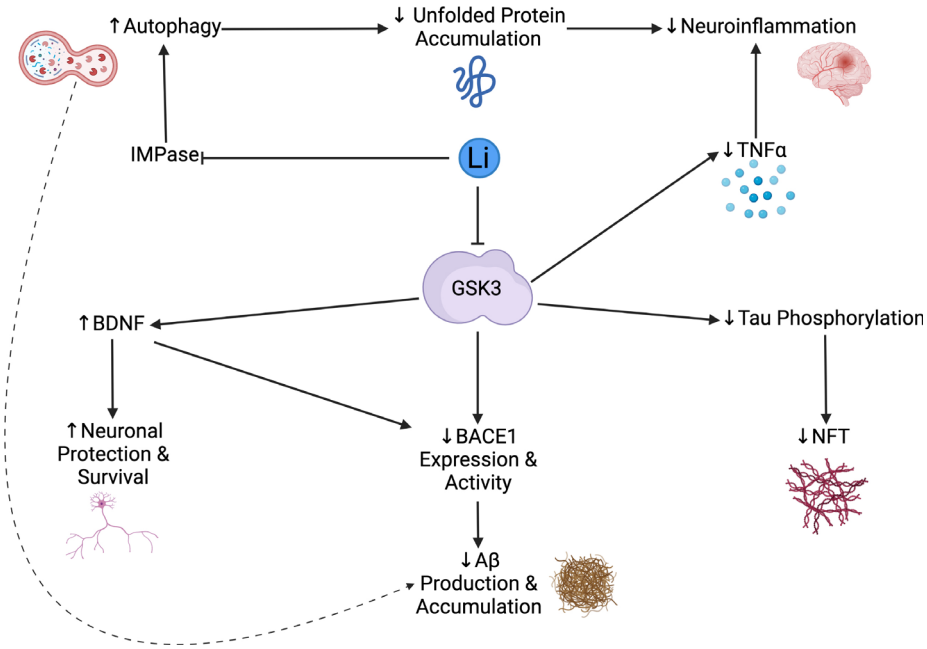

Fig. (4). Neuroprotective effects of low-dose lithium treatment. By inhibiting GSK3 activity in the brain, low-dose Li reduces the formation of neurofibrillary tangles (NFT) and amyloid beta (Aβ) production and accumulation, while also reducing neuroinflammation and promoting expression of neuroprotective brain-derived neurotrophic factor (BDNF) to support neuronal function and survival. Low-dose Li also reduces neuroinflammation in a GSK3-independent manner by increasing autophagy and reducing the accumulation of unfolded proteins through inhibition of IMPase. Since autophagy also has a role in Aβ clearance, the enhancement of autophagy with Li may also help in lowering Aβ levels (dashed line). *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

develop later in life (age 65+) due to environmental, metabolic, viral, or genetic factors, and is known as sporadic AD [128]. Late-onset sporadic AD makes up more than 95% of AD cases [127]. The exact mechanisms that initiate AD pathogenesis are still largely unknown; however, the most well-known pathological processes involved are the development of Aβ plaques and hyperphosphorylation of tau protein, leading to a build-up of neurofibrillary tangles (NFT) commonly in the prefrontal cortex and hippocampus [129]. With a cure for AD remaining elusive and a global population that continues to age, it is imperative that researchers find ways to prevent and slow the progression of AD.

Li is well-known to have multiple neuroprotective effects that can be used against AD pathology. In fact, numerous studies in patients receiving Li for bipolar disorder have reported lower rates of dementias, including AD [9, 23, 130-132]. The neuroprotective effects of Li are pleiotropic, acting on several different pathways, and have been thoroughly reviewed elsewhere [133, 134]. In brief, Li can offer neuroprotection by inhibiting GSK3 and subsequent NFT formation; lowering Aβ levels through reductions in beta-secretase-1 (BACE-1) expression/activity and the promotion of autophagic clearance; increasing neuroprotective hormones, such as brain-derived neurotrophic factor (BDNF); and lowering inflammation and oxidative stress (Fig. **4**) [133-137]. Furthermore, the insulin-mimetic effects of Li could also be of benefit, as those with metabolic disorders, such as obesity and T2DM, are at higher risk of developing neurocognitive disorders, such as AD [138]. Many consider AD to be a metabolic disorder with impairments in glucose and insulin regulation, often referring to AD as type 3 diabetes [139].

5.1. Low-Dose Li and Alzheimer's Pathology

While cognitive benefits have been observed in patients undergoing Li therapy, there have been studies that show the therapeutic potential of low-dose Li for AD [9, 140-143]. Using an ecological approach, we and others have shown negative associations between trace Li in tap water and Alzheimer's disease mortality [7, 144, 145]. In a nested case-control study performed by Kessing *et al.*, the authors found an increase in AD incidence rate ratio (IRR) with Li exposure in drinking water ranging from 0.5-10 µg/L; however, when Li exposure in drinking water increased above 10.1 µg/L, there were subsequent decreases in the IRR [145]. Although, in another recent report conducted in the U.S., groundwater Li levels were not associated with rates of dementia after controlling for local health care resources and other demographics, thereby questioning whether trace amounts of Li can really exert a neuroprotective effect and prevent/slow the progression of AD [146]. This stresses the need for future studies that systematically examine the effects of low-dose Li on AD and dementia using randomized controlled trials and longitudinal approaches.

One study conducted in 2013 by Nunes *et al.* evaluated the effects of microdose (300µg/day) Li treatment on cognitive function in patients with AD over 15 months. They observed no changes in mini-mental state examination (MMSE) among Li-treated patients compared to control patients who exhibited progressive declines in MMSE scores throughout the study [142]. Although serum [Li] was not measured given that Li was provided in the microgram level, the serum concentrations of Li would presumably be well below the therapeutic range. Thus, it appears as though low-

dose Li can provide a stabilizing effect that delays the progression of AD. In a later study by Nunes and colleagues, they treated the J20 mouse model of AD (characterized by progressive amyloid deposition) with a microdose of Li (0.25 mg/kg/day) for either 16 months (starting at 2 months of age) or 10 months (starting at 8 months of age). Interestingly, both WT and J20 mice treated with the microdose of Li (10 and 16 months) had improved spatial memory as assessed by Barnes maze and elevated plus maze [147]. Moreover, they found that starting the Li microdose treatment at 2 months of age had a more profound effect of attenuating the formation of senile plaques, neuronal loss in the prefrontal cortex and hippocampus, while also increasing BDNF in the cortex [147]. Therefore, at least in rodents, microdose Li can be used to prevent and slow AD pathology.

In another study conducted by Wilson and colleagues using the McGill-R-Thy1-APP transgenic rat model of AD, an even lower dose of Li (40 μg/kg) in a more bioavailable formulation known as NP03 was shown to provide neuroprotective effects [136]. NP03 is a reverse water-in-oil microemulsion which, when administered *via* the transmucosal route, avoids breakdown *via* the gastrointestinal and hepatic systems, making the contained lithium dose more available to the central nervous system [148]. Transgenic rats were treated during the early pre-plaque development phase (started at 3 months of age and treated for 8 weeks) when Aβ peptides begin accumulating in the intraneuronal compartment, thereby disrupting synaptic plasticity. NP03 Li-treated rats demonstrated salvaged novel object recognition and fear memory as well as reduced spatial learning impairments induced by Aβ accumulation compared to vehicle-treated transgenic rats. The authors also observed recovered levels of inhibitory phosphorylation of GSK3β relative to total GSK3β, as well as reduced *Bace1* mRNA and BACE1 activity levels, leading to lowered levels of neurotoxic Aβ [136]. In another recent study, Wilson *et al.* evaluated the effects of the NP03 Li microdose formulation in older McGill-R-Thy1-APP transgenic rats, where they started treatment at 13 months of age for a total of 12 weeks [143]. As with younger transgenic rats, NP03 rescued impairments in novel object memory and lowered levels of neurotoxic Aβ. In addition, the authors found that NP03 reduced markers of neuroinflammation and oxidative stress in the transgenic rats, which altogether suggests that microdose Li, in the form of NP03, is effective in both young and old transgenic rats, thus preventing and treating AD.

5.2. The Effect of Exercise and Low-Dose Li on Neuroprotection

Not surprisingly, exercise can prevent and even counteract cognitive decline, and physical inactivity is a major risk factor for the development of AD [149-151]. The neuroprotective effects of exercise, like Li, can occur through several pathways, including but not limited to improvements in glucose regulation and insulin signalling [149, 150, 152, 153], increases in BDNF expression [149], and reductions in oxidative stress and inflammation [150]. The fact that Li and regular exercise appear to act on similar pathways raises the possibility that Li may mimic or perhaps amplify the effects of exercise. Although this is still an evolving concept, a recent study has shown a potential benefit of the combined therapies in combatting neurodegeneration associated with high-fat feeding. In this study, 10-week old male Sprague-Dawley rats were fed a high-fat diet (HFD) for 8 weeks to induce obesity and then treated with low-dose Li (10 mg/kg/day) alone, exercise alone, or Li and exercise for 12 weeks [154]. Similar to Jung *et al.* [99], 12 weeks of Li treatment or endurance exercise significantly reduced body and fat mass, reinforcing the notion that low-dose Li may mimic this effect of exercise [154]. Moreover, Li or exercise significantly increased the expression of the neuroprotective factor BDNF in the hippocampus compared to chow-fed and HFD-fed controls, and together Li and exercise provided a synergistic effect, further increasing BDNF expression. However, cognitive tests were not conducted, and as such, whether this effect translated to improved cognitive function remains unknown. Therefore, future studies should examine further whether low-dose Li can mimic and/or amplify the effects of regular exercise on cognitive function.

5.3. Summary of the Effect of Li on Alzheimer's Disease

Due to the psychiatric uses of Li, there has been more research in the area of low-dose Li treatment and cognitive function compared to other areas. These findings have shown that Li treatment is capable of mitigating AD pathogenesis even at microdoses in animal models and preventing associated cognitive decline in human studies. This occurs mainly through lithium's inhibitory effects on GSK3β activity and associated antioxidant and autophagic-enhancing effects, which reduce the accumulation of NFT and Aβ plaques (Fig. **4**). There is also a potential for combined low-dose Li and exercise therapy to improve the metabolic dysregulation associated with AD pathology and pathogenesis as well as providing a synergistic neuroprotective effect on cognitive function; however, this requires more investigation.

6. LOW-DOSE LI, INFLAMMAGING AND OXIDATIVE STRESS

In all of the age-related diseases that we have reviewed so far, oxidative stress and inflammation have been involved in disease progression, with likely contributions to etiology as well. Processes involved in inflammation and oxidative stress increase with age as our bodies lose the ability to properly reduce levels of reactive oxygen/nitrogen species (RONS) and inflammatory mediators [155]. Li has long been known to exert pleiotropic effects, including lowering inflammation and oxidative stress [133, 156, 157], which we hypothesize to promote cellular resilience against aging.

6.1. Low-Dose Li and Inflammaging

Inflammaging is a state of chronic-low grade inflammation that is commonly found in aged individuals [158]. It is a form of sterile inflammation that occurs in the absence of infection and can cause tissue damage and degeneration, ultimately worsening the outcomes associated with CVD, sarcopenia, osteoporosis, T2DM, T1D, and neurodegenerative diseases, such as AD [158, 159]. The main inflammatory cytokines detected to be upregulated with aging and age-related diseases include interleukin-1beta (IL-1β), IL-6, and tumour necrosis factor-alpha (TNF-α) [158, 159]. Inflammaging can be sourced from adipocytes and the increased adiposity associated with aging [160], as well as an increased

presence of senescent cells. Cellular senescence is a process where cells cease dividing and undergo distinctive phenotypic alterations [161]. Namely, senescent cells will take on a senescence-associated secretory phenotype (SASP), where they produce and secrete inflammatory cytokines and other mediators in an attempt to rid the tissue/organ of these non-functional cells [162]. In addition to replicative senescence, non-replicative senescence can also be detected in post-mitotic cells in aged individuals as damage to DNA accumulates [163]. In both replicative and non-replicative senescence, the ability of the body to clear these cells in response to the SASP and heightened basal inflammation becomes impaired as we age, ultimately contributing to the phenomenon termed inflammaging.

The anti-inflammatory effects of Li occur primarily through its inhibition of GSK3, though GSK3-independent effects may also play a role. Briefly, the inhibition of GSK3 *via* Li represses both the nuclear factor (NF)-κB and signal transducer and activator of transcription (STAT) pathways, ultimately lowering the expression of, and sensitivity to, inflammatory cytokines and mediators, including IL-1β, IL-6, TNF-α, inducible nitric oxide synthase (iNOS), prostaglandin E2 and cyclooxygenase-2. In addition to reducing these pro-inflammatory mediators, others have shown that Li can promote the production of anti-inflammatory cytokines, such as IL-10, in response to lipopolysaccharide [164]. Importantly, most studies examining the anti-inflammatory effects of Li have typically used therapeutic or supra-therapeutic doses of Li, with only a few studies using low doses. In the study by Wilson *et al.*, using the NP03 microdose Li formulation (40 μg/kg) in the rat model of AD, the authors reported decreased hippocampal levels of IL-6 and chemokine CXCL1, which is transcriptionally regulated by IL-6 [143]. CXCL1 acts as a chemoattractant for other immune cells, such as monocytes and neutrophils, which contribute to the inflammatory response. The mechanism proposed to be responsible for this observed effect was through the inhibition of GSK3β with Li leading to the inactivation of NF-κB and STAT3 transcriptional activity [143]. In another recent study, microdose Li treatment reduced cellular senescence and the SASP in human astrocytes [165]. Here, Viel *et al.* also demonstrated that microdose Li suppressed amyloid β-induced cellular senescence in astrocytes, further supporting the beneficial effect of low-dose Li on AD and strengthening the Li-sensitive linkages between inflammation and AD. In all, low-dose Li has a strong potential to attenuate inflammaging; however, this needs to be examined further in future studies.

6.2. Low-Dose Li and Oxidative Stress

RONS are critical signalling molecules that regulate several physiological functions, such as insulin synthesis, vascular tone, cell proliferation, differentiation, and migration [166]. However, in an uncontrolled state, these unpaired free radicals steal electrons from proteins, lipids and other molecules, perpetuating a state of oxidative stress. It is well established that oxidative stress contributes to the development of a number of diseases, particularly age-related diseases [166]; therefore, attenuating oxidative stress may improve upon many physiological outcomes as we age. In patients with bipolar disorder, Li treatment significantly reduces the levels of plasma lipid peroxides and improves antioxidant status [157, 167]. Mechanistically, this can occur through the effect of therapeutic Li on improving mitochondrial function in patients with bipolar disorder, leading to reductions in RONS production and oxidative stress [168, 169]. Moreover, through its inhibition of GSK3, Li can also exert resilience against RONS by increasing the production of anti-oxidant systems, such as chaperone proteins, heme oxgyenase-1 (HO-1), glutathione, and the activity of glutathione transferase [124, 170-174].

With respect to low-dose Li, our lab has shown that feeding young male C57BL/6J mice with 10 mg/kg/day of Li for 6 weeks increased protein levels of heat shock protein 70 (Hsp70) in cardiac tissue [33]. We presume that this was due to the inhibition of GSK3β, which, when active, negatively regulates the transcription factor heat shock factor-1 HSF-1 responsible for the transcription of Hsp70 [170]. Hsp70 is capable of binding to proteins and protecting their structures from misfolding or from cytotoxic damage induced from RONS-mediated post-translational modifications (*i.e.*, S-nitrosylation and T-nitration) [175]. The ability of Hsp70 to bind to and protect the SERCA pumps [176, 177] is of particular interest, as this could protect against age-related impairments in cardiac and skeletal muscle contractility. In addition to our study, others have shown that in a T1D mouse model induced by STZ injection, microdose Li protects against pancreatic oxidative stress and cell death by inhibiting GSK3β and activating nuclear factor erythroid 2-related factor 2 (Nrf2)-mediated transcription of HO-1 [124]. In fact, it is through this GSK3/Nrf2 pathway [178] that Li is thought to promote longevity [10, 179], which we contend adds further support to the notion that Li can provide cellular resilience against aging. In the study by Castillo-Quan *et al.*, the authors tested the effects of Li on *Drosophila* lifespan using Li concentrations that would result in tissue Li levels below 0.5 mM. When treated with this low dose of Li, they observed a life-prolonging effect; however, when Li exceeded this threshold, it became toxic and shortened the lifespan [178]. This highlights the fact that Li operates under hormesis and that its physiological benefits may be elicited at lower concentrations; however, this warrants future studies. It is also worth considering that RONS are important signalling molecules that also act under hormesis, where relatively small amounts of RONS and oxidative/nitrosative stress are in fact protective as they can ramp up physiological defense systems [180-182]. One classical example of this is in ischemic preconditioning, whereby brief episodes of ischemia and reperfusion trigger a transient rise in RONS that upregulate protective and adaptive mechanisms that protect the tissue against injury from a subsequent sustained ischemic event [183]. This preconditioning can increase the expression of protective genes, termed vitagenes, which include various antioxidant systems such as those already discussed here (Hsp70 and glutathione) [180]. In the context of Li, its RONS lowering effect may mitigate this important protective response observed with preconditioning. However, evidence within the literature suggests otherwise, where Li treatment appears to mimic the protective effect of preconditioning. In fact, several studies (many with low doses of Li) have shown that chronic Li treatment protects against ischemia-reperfusion damage in the brain, kidney, heart, and

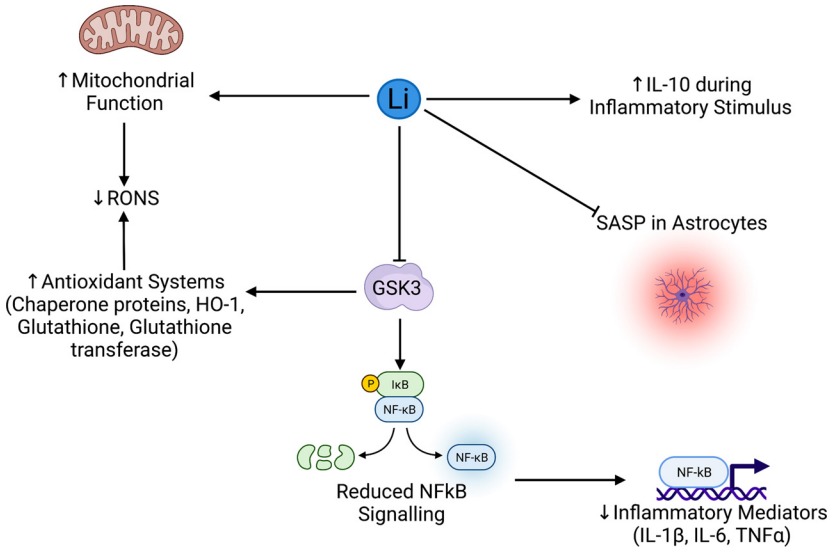

Fig. (5). Anti-inflammatory and antioxidant effects of low-dose lithium. Low-dose Li reduces the production of reactive oxygen/nitrogen species (RONS) by promoting healthy mitochondrial function. Low-dose Li can also reduce the senescence-associated secretory phenotype (SASP) in astrocytes and increases expression of anti-inflammatory cytokine IL-10 in the presence of inflammatory stimuli. By inhibiting GSK3, low-dose Li also reduces the expression of pro-inflammatory mediators and promotes upregulation of antioxidant systems, further reducing levels of RONS damage. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

liver [184-190]. Suggested pathways behind this well-established effect include the increased production of nitric oxide and the amplification of the NrF2 pathway, both of which are critical in the activation of the vitagene network [180, 182].

6.3. Summary of the Effects of Li on Inflammation and Oxidative Stress

Based on these mechanisms identified above, it is possible that low-dose Li treatment could promote an increase in cellular resilience, while providing anti-inflammatory and antioxidant protection during the natural process of aging (Fig. **5**). Although some studies have shown these beneficial effects in the brain, pancreas, and cardiac tissues with low-dose Li treatment, it is still largely unknown if low or sub-therapeutic doses are beneficial in all tissue types. Whether or not these effects can prevent or mitigate the development of chronic, low-grade inflammation is also yet to be determined. This line of questioning is still very novel and requires further in-depth investigation in various tissue types and biological models.

CONCLUSION

Modern medicine and technology have significantly prolonged human lifespan, and while beneficial, this has also equated to an increase in the prevalence of age-related diseases and disorders. As our global population continues to age, so do the rates of these disorders, highlighting the need for a shift to preventive strategies focused on enhancing healthspan, *i.e.*, the proportion of our lives in near-optimal health. In this review, we have highlighted the physiological benefits of low-dose Li and its potential ability to counteract various age-related disorders, such as CVD, sarcopenia, osteoporosis, AD, obesity, and T2DM. These effects of Li, some of which seem to mimic or even amplify regular exercise, appear to be mediated through both GSK3-dependent and GSK3-independent pathways. Importantly, the primary intention of our review was to highlight the potential benefits of low-dose Li that are perhaps underappreciated due to the stigma associated with high-dose Li therapy and Li toxicity. It should also be highlighted that the studies reviewed here primarily use animal models or show correlational data, identifying a possible relationship between lithium levels in humans and potential health benefits. Though promising, we envision that this review could act as a call for future studies that will more formally investigate the potential effects (good or bad) of low-dose Li on human health throughout the lifespan. Future areas of research in human or preclinical models could test the effects of Li on aging, other age-related diseases, the influence of biological sex, and the impact of combining healthy behaviours, such as diet and exercise, as we move toward identifying paths to optimizing healthspan as we age.

LIST OF ABBREVIATIONS

AD	=	Alzheimer's Disease
AHD	=	Atherosclerotic Heart Disease
APOE	=	Apolipoprotein E
AV	=	Atrioventricular
Aβ	=	Amyloid Beta
BACE-1	=	Beta-secretase-1
BDNF	=	Brain-derived Neurotrophic Factor
BMD	=	Bone Mineral Density
BMI	=	Body Mass Index
Ca^{2+}	=	Calcium
cAMP	=	Cyclic Adenosine Monophosphate
CMNCs	=	Cultured mouse neonatal cardiomyocytes

CTX	=	Beta-isomerized Carboxyterminal Cross-Linking Telopeptides
CVD	=	Cardiovascular Disease
ER	=	Endoplasmic Reticulum
FFA	=	Free Fatty Acids
FZD	=	Frizzled
GLUT4	=	Glucose Transporter 4
GPCRs	=	G-protein Coupled Receptors
GSK3β	=	Glycogen Synthase Kinase-3 beta
HDL	=	High-density Lipoprotein
HFD	=	High-fat Diet
HO-1	=	Heme Oxygenase-1
HSF-1	=	Heat Shock Factor-1
Hsp70	=	Heat Shock Protein 70
IGF-1	=	Insulin-like Growth Factor-1
IL1β	=	Interleukin-1 Beta
IMPase	=	Inositol Monophosphatase
iNOS	=	Inducible Nitric Oxide Synthase
IP3	=	Inositol-3,4,5-phosphate
IRR	=	Incidence Rate Ratio
K^+	=	Potassium
LDL	=	Low-density Lipoprotein
Li	=	Lithium
Mg^{2+}	=	Magnesium
MI	=	Myocardial Infarction
MMSE	=	Mini-mental State Examination
mTOR	=	Mammalian Target of Rapamycin
Na^+	=	Sodium
NF-κB	=	Nuclear Factor-kappa B
NFAT	=	Nuclear Factor of Activated T-cells
NFT	=	Neurofibrillary Tangles
NNAT	=	Neuronatin
NO	=	Nitric Oxide
NOS	=	Nitric Oxide Synthase
Nrf2	=	Nuclear Factor Erythroid 2-related Factor 2
OPG	=	Osteoprotegrin
P1NP	=	Procollagin Type 1 N-terminal Propeptide
PGC-1α	=	Peroxisome Proliferator-activated Receptor-gamma Coactivator-1 Alpha
PI3K	=	Phosphoinositide 3-kinase
PLN	=	Phospholamban
PTH	=	Parathyroid Hormone
RANKL	=	Receptor Activator of Nuclear Factor-kappa B
RONS	=	Reactive Oxygen/Nitrogen Species
SA	=	Sinoatrial
SASP	=	Senescence-associated Secretory Phenotype
SERCA	=	Sarco(endo)plasmic reticulum Ca^{2+}-ATPase
SLN	=	Sarcolipin
SR	=	Sarcoplasmic Reticulum
STAT	=	Signal Transducer and Activator of Transcription
STZ	=	Streptozotocin
T1D	=	Type 1 Diabetes
T2DM	=	Type 2 Diabetes Mellitus
TNF-α	=	Tumour Necrosis Factor-alpha
UCP1	=	Uncoupling Protein 1
VCAM-1	=	Vascular Adhesion Molecule-1
WT	=	Wild-type

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Szklarska, D.; Rzymski, P. Is lithium a micronutrient? From biological activity and epidemiological observation to food fortification. *Biol. Trace Elem. Res.,* **2019**, *189*(1), 18-27. http://dx.doi.org/10.1007/s12011-018-1455-2 PMID: 30066063

[2] Medić, B.; Stojanović, M.; Stimec, B.V.; Divac, N.; Vujović, K.S.; Stojanović, R.; Čolović, M.; Krstić, D.; Prostran, M. Lithium - pharmacological and toxicological aspects: The current state of the art. *Curr. Med. Chem.,* **2020**, *27*(3), 337-351. http://dx.doi.org/10.2174/0929867325666180904124733 PMID: 30182841

[3] Dudev, T.; Mazmanian, K.; Weng, W.H.; Grauffel, C.; Lim, C. Free and bound therapeutic lithium in brain signaling. *Acc. Chem. Res.,* **2019**, *52*(10), 2960-2970. http://dx.doi.org/10.1021/acs.accounts.9b00389 PMID: 31556294

[4] Marmol, F. Lithium: Bipolar disorder and neurodegenerative diseases possible cellular mechanisms of the therapeutic effects of lithium. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2008**, *32*(8), 1761-1771. http://dx.doi.org/10.1016/j.pnpbp.2008.08.012 PMID: 18789369

[5] Oruch, R.; Elderbi, M.A.; Khattab, H.A.; Pryme, I.F.; Lund, A. Lithium: A review of pharmacology, clinical uses, and toxicity. *Eur. J. Pharmacol.,* **2014**, *740*, 464-473. http://dx.doi.org/10.1016/j.ejphar.2014.06.042 PMID: 24991789

[6] Schrauzer, G.N. Lithium: occurrence, dietary intakes, nutritional essentiality. *J. Am. Coll. Nutr.,* **2002**, *21*(1), 14-21. http://dx.doi.org/10.1080/07315724.2002.10719188 PMID: 11838882

[7] Baranowski, B.J.; Hayward, G.C.; Fajardo, V.A.; MacPherson, R.E.K. Increased prevalence of obesity/type 2 diabetes and lower levels of lithium in rural texas counties may explain greater Alzheimer's disease risk. *J. Alzheimers Dis.,* **2018**, *64*(1), 303-308. http://dx.doi.org/10.3233/JAD-171150 PMID: 29865052

[8] Fajardo, V.A.; Fajardo, V.A.; LeBlanc, P.J.; MacPherson, R.E.K. Examining the relationship between trace lithium in drinking water and the rising rates of age-adjusted Alzheimer's disease mortality in texas. *J. Alzheimers Dis.,* **2017**, *61*(1), 425-434. http://dx.doi.org/10.3233/JAD-170744 PMID: 29103043

[9] Mauer, S.; Vergne, D.; Ghaemi, S.N. Standard and trace-dose lithium: A systematic review of dementia prevention and other behavioral benefits. *Aust. N. Z. J. Psychiatry,* **2014**, *48*(9), 809-818. http://dx.doi.org/10.1177/0004867414536932 PMID: 24919696

[10] Fajardo, V.A.; LeBlanc, P.J.; Fajardo, V.A. Trace lithium in Texas tap water is negatively associated with all-cause mortality and premature death. *Appl. Physiol. Nutr. Metab.,* **2018**, *43*(4), 412-414. http://dx.doi.org/10.1139/apnm-2017-0653 PMID: 29206474

[11] Hamstra, S.I.; Kurgan, N.; Baranowski, R.W.; Qiu, L.; Watson, C.J.F.; Messner, H.N.; MacPherson, R.E.K.; MacNeil, A.J.; Roy, B.D.; Fajardo, V.A. Low‐dose lithium feeding increases the SERCA2a‐to‐phospholamban ratio, improving SERCA function in murine left ventricles. *Exp. Physiol.,* **2020**, *105*(4), 666-675. http://dx.doi.org/10.1113/EP088061 PMID: 32087034

[12] Ahmad, F.B.; Anderson, R.N. The leading causes of death in the US for 2020. *JAMA,* **2021**, *325*(18), 1829-1830. http://dx.doi.org/10.1001/jama.2021.5469 PMID: 33787821

[13] Statistics Canada. Table 13-10-0394-01 Leading causes of death, total population, by age group. **2021**. Available from: https://www150.statscan.gc.ca/t1/tbl1/en/tv.action?pid=13100394 01 [Accessed on: 1st September, 2021].

[14] Nakamura, M.; Sadoshima, J. Mechanisms of physiological and pathological cardiac hypertrophy. *Nat. Rev. Cardiol.,* **2018**, *15*(7), 387-407. http://dx.doi.org/10.1038/s41569-018-0007-y PMID: 29674714

[15] Mehta, N.; Vannozzi, R. Lithium-induced electrocardiographic changes: A complete review. *Clin. Cardiol.,* **2017**, *40*(12), 1363-1367. http://dx.doi.org/10.1002/clc.22822 PMID: 29247520

[16] Linask, K.K.; Huhta, J. Folate protection from congenital heart defects linked with canonical Wnt signaling and epigenetics. *Curr. Opin. Pediatr.,* **2010**, *22*(5), 561-566. http://dx.doi.org/10.1097/MOP.0b013e32833e2723 PMID: 20844350

[17] Patorno, E.; Huybrechts, K.F.; Bateman, B.T.; Cohen, J.M.; Desai, R.J.; Mogun, H.; Cohen, L.S.; Hernandez-Diaz, S. Lithium use in pregnancy and the risk of cardiac malformations. *N. Engl. J. Med.,* **2017**, *376*(23), 2245-2254. http://dx.doi.org/10.1056/NEJMoa1612222 PMID: 28591541

[18] Moradi, S.; Aminian, A.; Abdollahi, A.; Jazayeri, A.; Ghamami, G.; Nikoui, V.; Bakhtiarian, A.; Jazaeri, F. Cardiac chronotropic hypo-responsiveness and atrial fibrosis in rats chronically treated with lithium. *Auton. Neurosci.,* **2019**, *216*, 46-50. http://dx.doi.org/10.1016/j.autneu.2018.09.002 PMID: 30241725

[19] McMullen, J.R.; Jennings, G.L. Differences between pathological and physiological cardiac hypertrophy: Novel therapeutic strategies to treat heart failure. *Clin. Exp. Pharmacol. Physiol.,* **2007**, *34*(4), 255-262. http://dx.doi.org/10.1111/j.1440-1681.2007.04585.x PMID: 17324134

[20] Shimizu, I.; Minamino, T. Physiological and pathological cardiac hypertrophy. *J. Mol. Cell. Cardiol.,* **2016**, *97*, 245-262. http://dx.doi.org/10.1016/j.yjmcc.2016.06.001 PMID: 27262674

[21] Molkentin, J.D.; Lu, J.R.; Antos, C.L.; Markham, B.; Richardson, J.; Robbins, J.; Grant, S.R.; Olson, E.N. A calcineurin-dependent transcriptional pathway for cardiac hypertrophy. *Cell,* **1998**, *93*(2), 215-228. http://dx.doi.org/10.1016/S0092-8674(00)81573-1 PMID: 9568714

[22] Ösby, U.; Brandt, L.; Correia, N.; Ekbom, A.; Sparén, P. Excess mortality in bipolar and unipolar disorder in Sweden. *Arch. Gen. Psychiatry,* **2001**, *58*(9), 844-850. http://dx.doi.org/10.1001/archpsyc.58.9.844 PMID: 11545667

[23] Prosser, J.M.; Fieve, R.R. Patients receiving lithium therapy have a reduced prevalence of neurological and cardiovascular disorders. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2016**, *71*, 39-44. http://dx.doi.org/10.1016/j.pnpbp.2016.06.006 PMID: 27328427

[24] Lee, T.M.; Lin, S.Z.; Chang, N.C. Effect of lithium on ventricular remodelling in infarcted rats *via* the Akt/mTOR signalling pathways. *Biosci. Rep.,* **2017**, *37*(2), BSR20160257. http://dx.doi.org/10.1042/BSR20160257 PMID: 28115595

[25] Milanesi, E.; Hadar, A.; Maffioletti, E.; Werner, H.; Shomron, N.; Gennarelli, M.; Schulze, T.G.; Costa, M.; Del Zompo, M.; Squassina, A.; Gurwitz, D. Insulin-like growth factor 1 differentially affects lithium sensitivity of lymphoblastoid cell lines from lithium responder and non-responder bipolar disorder patients. *J. Mol. Neurosci.,* **2015**, *56*(3), 681-687. http://dx.doi.org/10.1007/s12031-015-0523-8 PMID: 25740013

[26] Klein, P.S.; Melton, D.A. A molecular mechanism for the effect of lithium on development. *Proc. Natl. Acad. Sci. USA,* **1996**, *93*(16), 8455-8459. http://dx.doi.org/10.1073/pnas.93.16.8455 PMID: 8710892

[27] Hermida, M.A.; Dinesh Kumar, J.; Leslie, N.R. GSK3 and its interactions with the PI3K/AKT/mTOR signalling network. *Adv. Biol. Regul.,* **2017**, *65*, 5-15. http://dx.doi.org/10.1016/j.jbior.2017.06.003 PMID: 28712664

[28] Beurel, E.; Grieco, S.F.; Jope, R.S. Glycogen synthase kinase-3 (GSK3): Regulation, actions, and diseases. *Pharmacol. Ther.,* **2015**, *148*, 114-131. http://dx.doi.org/10.1016/j.pharmthera.2014.11.016 PMID: 25435019

[29] Freland, L.; Beaulieu, J.-M. Inhibition of GSK3 by lithium, from single molecules to sig-naling networks. *Front Mol Neurosci,* **2012**, *5*, 14. http://dx.doi.org/10.3389/fnmol.2012.00014

[30] Hardt, S.E.; Sadoshima, J. Glycogen synthase kinase-3β: a novel regulator of cardiac hypertrophy and development. *Circ. Res.,* **2002**, *90*(10), 1055-1063. http://dx.doi.org/10.1161/01.RES.0000018952.70505.F1 PMID: 12039794

[31] Badorff, C.; Ruetten, H.; Mueller, S.; Stahmer, M.; Gehring, D.; Jung, F.; Ihling, C.; Zeiher, A.M.; Dimmeler, S. Fas receptor signaling inhibits glycogen synthase kinase 3β and induces cardiac hypertrophy following pressure overload. *J. Clin. Invest.,* **2002**, *109*(3), 373-381. http://dx.doi.org/10.1172/JCI13779 PMID: 11827997

[32] Vetter, R.; Rehfeld, U.; Reissfelder, C.; Weiß, W.; Wagner, K.D.; Günther, J.; Hammes, A.; Tschöpe, C.; Dillmann, W.; Paul, M. Transgenic overexpression of the sarcoplasmic reticulum Ca^{2+} ATPase improves reticular Ca^{2+} handling in normal and diabetic rat hearts. *FASEB J.,* **2002**, *16*(12), 1657-1659. http://dx.doi.org/10.1096/fj.01-1019fje PMID: 12206992

[33] Hamstra, S.I.; Whitley, K.C.; Baranowski, R.W.; Kurgan, N.; Braun, J.L.; Messner, H.N.; Fajardo, V.A. The role of phospholamban and GSK3 in regulating rodent cardiac SERCA function. *Am. J. Physiol. Cell Physiol.,* **2020**, *319*(4), C694-C699. http://dx.doi.org/10.1152/ajpcell.00318.2020 PMID: 32755452

[34] Lazzara, C.A.; Kim, Y.H. Potential application of lithium in Parkinson's and other neurodegenerative diseases. *Front. Neurosci.,* **2015**, *9*, 403. http://dx.doi.org/10.3389/fnins.2015.00403 PMID: 26578864

[35] Teng, A.C.T.; Miyake, T.; Yokoe, S.; Zhang, L.; Rezende, L.M., Jr; Sharma, P.; MacLennan, D.H.; Liu, P.P.; Gramolini, A.O. Metformin increases degradation of phospholamban *via* autophagy in cardiomyocytes. *Proc. Natl. Acad. Sci. USA,* **2015**, *112*(23), 7165-7170. http://dx.doi.org/10.1073/pnas.1508815112 PMID: 26040000

[36] Takahashi-Yanaga, F. Roles of glycogen synthase kinase-3 (GSK-3) in cardiac development and heart disease. *J. UOEH,* **2018**, *40*(2), 147-156. http://dx.doi.org/10.7888/juoeh.40.147 PMID: 29925734

[37] Tateishi, A.; Matsushita, M.; Asai, T.; Masuda, Z.; Kuriyama, M.; Kanki, K.; Ishino, K.; Kawada, M.; Sano, S.; Matsui, H. Effect of

inhibition of glycogen synthase kinase-3 on cardiac hypertrophy during acute pressure overload. *Gen. Thorac. Cardiovasc. Surg.,* **2010**, *58*(6), 265-270.
http://dx.doi.org/10.1007/s11748-009-0505-2 PMID: 20549454

[38] Nedeljkovic, Z.S.; Gokce, N.; Loscalzo, J. Mechanisms of oxidative stress and vascular dysfunction. *Postgrad. Med. J.,* **2003**, *79*(930), 195-200.
http://dx.doi.org/10.1136/pmj.79.930.195 PMID: 12743334

[39] Förstermann, U. Oxidative stress in vascular disease: causes, defense mechanisms and potential therapies. *Nat. Clin. Pract. Cardiovasc. Med.,* **2008**, *5*(6), 338-349.
http://dx.doi.org/10.1038/ncpcardio1211 PMID: 18461048

[40] Mikhed, Y.; Daiber, A.; Steven, S. Mitochondrial oxidative stress, mitochondrial DNA damage and their role in age-related vascular dysfunction. *Int. J. Mol. Sci.,* **2015**, *16*(7), 15918-15953.
http://dx.doi.org/10.3390/ijms160715918 PMID: 26184181

[41] Voors, A.W. Does lithium depletion cause atherosclerotic heart-disease? *Lancet,* **1969**, *294*(7634), 1337-1339.
http://dx.doi.org/10.1016/S0140-6736(69)90868-X PMID: 4188097

[42] Voors, A.W. Lithium depletion and atherosclerotic heart-disease. *Lancet,* **1970**, *296*(7674), 670.
http://dx.doi.org/10.1016/S0140-6736(70)91446-7 PMID: 4195811

[43] Choi, S.E.; Jang, H.J.; Kang, Y.; Jung, J.G.; Han, S.J.; Kim, H.J.; Kim, D.J.; Lee, K.W. Atherosclerosis induced by a high-fat diet is alleviated by lithium chloride *via* reduction of VCAM expression in ApoE-deficient mice. *Vascul. Pharmacol.,* **2010**, *53*(5-6), 264-272.
http://dx.doi.org/10.1016/j.vph.2010.09.004 PMID: 20888430

[44] Tabas, I. Cellular Cholesterol Metabolism in Health and Disease. In: *Molecular basis of cardiovascular disease: A companion to Braunwald's Heart Disease,* 2nd ed; WB Saunders Company: Chien, K.R., **2004**; pp. 414-431.

[45] Seals, D.R.; Jablonski, K.L.; Donato, A.J. Aging and vascular endothelial function in humans. *Clin. Sci. (Lond.),* **2011**, *120*(9), 357-375.
http://dx.doi.org/10.1042/CS20100476 PMID: 21244363

[46] Bosche, B.; Molcanyi, M.; Rej, S.; Doeppner, T.R.; Obermann, M.; Müller, D.J.; Das, A.; Hescheler, J.; Macdonald, R.L.; Noll, T.; Härtel, F.V. Low-dose lithium stabilizes human endothelial barrier by decreasing MLC phosphorylation and universally augments cholinergic vasorelaxation capacity in a direct manner. *Front. Physiol.,* **2016**, *7*, 593.
http://dx.doi.org/10.3389/fphys.2016.00593 PMID: 27999548

[47] Afsharimani, B.; Moezi, L.; Sadeghipour, H.; Rahimzadeh-Rofouyi, B.; Nobakht, M.; Sanatkar, M.; Ghahremani, M.H.; Dehpour, A.R. Effect of chronic lithium administration on endothelium-dependent relaxation of rat mesenteric bed: role of nitric oxide. *Can. J. Physiol. Pharmacol.,* **2007**, *85*(10), 1038-1046.
http://dx.doi.org/10.1139/Y07-095 PMID: 18066105

[48] Rahimzadeh-Rofouyi, B.; Afsharimani, B.; Moezi, L.; Ebrahimi, F.; Mehr, S.E.; Mombeini, T.; Ghahremani, M.H.; Dehpour, A.R. Role of nitric oxide and prostaglandin systems in lithium modulation of acetylcholine vasodilation. *J. Cardiovasc. Pharmacol.,* **2007**, *50*(6), 641-646.
http://dx.doi.org/10.1097/FJC.0b013e318153f262 PMID: 18091580

[49] Bosche, B.; Molcanyi, M.; Noll, T.; Rej, S.; Zatschler, B.; Doeppner, T.R.; Hescheler, J.; Müller, D.J.; Macdonald, R.L.; Härtel, F.V. A differential impact of lithium on endothelium-dependent but not on endothelium-independent vessel relaxation. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2016**, *67*, 98-106.
http://dx.doi.org/10.1016/j.pnpbp.2016.02.004 PMID: 26875501

[50] Aoyagi, M.; Arvai, A.S.; Tainer, J.A.; Getzoff, E.D. Structural basis for endothelial nitric oxide synthase binding to calmodulin. *EMBO J.,* **2003**, *22*(4), 766-775.
http://dx.doi.org/10.1093/emboj/cdg078 PMID: 12574113

[51] McGuigan, F.E.; Bartosch, P.; Åkesson, K.E. Musculoskeletal health and frailty. *Best Pract. Res. Clin. Rheumatol.,* **2017**, *31*(2), 145-159.
http://dx.doi.org/10.1016/j.berh.2017.11.002 PMID: 29224693

[52] Tu, K.N.; Lie, J.D.; Wan, C.K.V.; Cameron, M.; Austel, A.G.; Nguyen, J.K.; Van, K.; Hyun, D. Osteoporosis: A review of treatment options. *P&T,* **2018**, *43*(2), 92-104.
PMID: 29386866

[53] Armas, L.A.G.; Recker, R.R. Pathophysiology of Osteoporosis. *Endocrinol. Metab. Clin. North Am.,* **2012**, *41*(3), 475-486.
http://dx.doi.org/10.1016/j.ecl.2012.04.006 PMID: 22877425

[54] Osteoporosis Facts and Statistics. Osteoporosis Canada. **2021**. Available from: https://osteoporosis.ca/fast-facts/ [Accessed on: 20th November, 2021].

[55] McGarry, K.A.; Kiel, D.P. Postmenopausal osteoporosis. *Postgrad. Med.,* **2000**, *108*(3), 79-91, 85-88, 91.
http://dx.doi.org/10.3810/pgm.2000.09.1.1206 PMID: 11004937

[56] Ogawa, S.; Yakabe, M.; Akishita, M. Age-related sarcopenia and its pathophysiological bases. *Inflamm. Regen.,* **2016**, *36*(1), 17.
http://dx.doi.org/10.1186/s41232-016-0022-5 PMID: 29259690

[57] Phillips, S.M. Nutritional supplements in support of resistance exercise to counter age-related sarcopenia. *Adv. Nutr.,* **2015**, *6*(4), 452-460.
http://dx.doi.org/10.3945/an.115.008367 PMID: 26178029

[58] Marty, E.; Liu, Y.; Samuel, A.; Or, O.; Lane, J. A review of sarcopenia: Enhancing awareness of an increasingly prevalent disease. *Bone,* **2017**, *105*, 276-286.
http://dx.doi.org/10.1016/j.bone.2017.09.008 PMID: 28931495

[59] Cohen, O.; Rais, T.; Lepkifker, E.; Vered, I. Lithium carbonate therapy is not a risk factor for osteoporosis. *Horm. Metab. Res.,* **1998**, *30*(9), 594-597.
http://dx.doi.org/10.1055/s-2007-978939 PMID: 9808330

[60] Lewicki, M.; Paez, H.; Mandalunis, P.M. Effect of lithium carbonate on subchondral bone in sexually mature Wistar rats. *Exp. Toxicol. Pathol.,* **2006**, *58*(2-3), 197-201.
http://dx.doi.org/10.1016/j.etp.2006.06.003 PMID: 16846729

[61] Wong, S.K.; Chin, K.Y.; Ima-Nirwana, S. The skeletal-protecting action and mechanisms of action for mood-stabilizing drug lithium chloride: current evidence and future potential research areas. *Front. Pharmacol.,* **2020**, *11*, 430.
http://dx.doi.org/10.3389/fphar.2020.00430 PMID: 32317977

[62] Kurgan, N.; Bott, K.N.; Helmeczi, W.E.; Roy, B.D.; Brindle, I.D.; Klentrou, P.; Fajardo, V.A. Low dose lithium supplementation activates Wnt/β-catenin signalling and increases bone OPG/RANKL ratio in mice. *Biochem. Biophys. Res. Commun.,* **2019**, *511*(2), 394-397.
http://dx.doi.org/10.1016/j.bbrc.2019.02.066 PMID: 30791983

[63] Kim, J.H.; Liu, X.; Wang, J.; Chen, X.; Zhang, H.; Kim, S.H.; Cui, J.; Li, R.; Zhang, W.; Kong, Y.; Zhang, J.; Shui, W.; Lamplot, J.; Rogers, M.R.; Zhao, C.; Wang, N.; Rajan, P.; Tomal, J.; Statz, J.; Wu, N.; Luu, H.H.; Haydon, R.C.; He, T.C. Wnt signaling in bone formation and its therapeutic potential for bone diseases. *Ther. Adv. Musculoskelet. Dis.,* **2013**, *5*(1), 13-31.
http://dx.doi.org/10.1177/1759720X12466608 PMID: 23514963

[64] Spencer, G.J.; Utting, J.C.; Etheridge, S.L.; Arnett, T.R.; Genever, P.G. Wnt signalling in osteoblasts regulates expression of the receptor activator of NFκB ligand and inhibits osteoclastogenesis *in vitro*. *J. Cell Sci.,* **2006**, *119*(7), 1283-1296.
http://dx.doi.org/10.1242/jcs.02883 PMID: 16522681

[65] Canalis, E. Wnt signalling in osteoporosis: mechanisms and novel therapeutic approaches. *Nat. Rev. Endocrinol.,* **2013**, *9*(10), 575-583.
http://dx.doi.org/10.1038/nrendo.2013.154 PMID: 23938284

[66] Clément-Lacroix, P.; Ai, M.; Morvan, F.; Roman-Roman, S.; Vayssière, B.; Belleville, C.; Estrera, K.; Warman, M.L.; Baron, R.; Rawadi, G. Lrp5-independent activation of Wnt signaling by lithium chloride increases bone formation and bone mass in mice. *Proc. Natl. Acad. Sci. USA,* **2005**, *102*(48), 17406-17411.
http://dx.doi.org/10.1073/pnas.0505259102 PMID: 16293698

[67] Vachhani, K.; Whyne, C.; Wang, Y.; Burns, D.M.; Nam, D. Low-dose lithium regimen enhances endochondral fracture healing in osteoporotic rodent bone. *J. Orthop. Res.,* **2018**, *36*(6), 1783-1789.
http://dx.doi.org/10.1002/jor.23799 PMID: 29106746

[68] Vachhani, K.; Pagotto, A.; Wang, Y.; Whyne, C.; Nam, D. Design of experiments confirms optimization of lithium administration parameters for enhanced fracture healing. *J. Biomech.,* **2018**, *66*, 153-158.
http://dx.doi.org/10.1016/j.jbiomech.2017.09.043 PMID: 29162229

[69] Woo, J. Sarcopenia. *Clin. Geriatr. Med.,* **2017**, *33*(3), 305-314.
http://dx.doi.org/10.1016/j.cger.2017.02.003 PMID: 28689564

[70] Rommel, C.; Bodine, S.C.; Clarke, B.A.; Rossman, R.; Nunez, L.; Stitt, T.N.; Yancopoulos, G.D.; Glass, D.J. Mediation of IGF-1-induced skeletal myotube hypertrophy by PI(3)K/Akt/mTOR and PI(3)K/Akt/GSK3 pathways. *Nat. Cell Biol.,* **2001**, *3*(11), 1009-1013. http://dx.doi.org/10.1038/ncb1101-1009 PMID: 11715022

[71] Verhees, K.J.P.; Schols, A.M.W.J.; Kelders, M.C.J.M.; Op den Kamp, C.M.H.; van der Velden, J.L.J.; Langen, R.C.J. Glycogen synthase kinase-3β is required for the induction of skeletal muscle atrophy. *Am. J. Physiol. Cell Physiol.,* **2011**, *301*(5), C995-C1007. http://dx.doi.org/10.1152/ajpcell.00520.2010 PMID: 21832246

[72] Mirzoev, T.M.; Sharlo, K.A.; Shenkman, B.S. The role of GSK-3β in the regulation of protein turnover, myosin phenotype, and oxidative capacity in skeletal muscle under disuse conditions. *Int. J. Mol. Sci.,* **2021**, *22*(10), 5081. http://dx.doi.org/10.3390/ijms22105081 PMID: 34064895

[73] Kurgan, N.; Whitley, K.C.; Maddalena, L.A.; Moradi, F.; Stoikos, J.; Hamstra, S.I.; Rubie, E.A.; Kumar, M.; Roy, B.D.; Woodgett, J.R.; Stuart, J.A.; Fajardo, V.A. A low-therapeutic dose of lithium inhibits GSK3 and enhances myoblast fusion in C2C12 cells. *Cells,* **2019**, *8*(11), 1340. http://dx.doi.org/10.3390/cells8111340 PMID: 31671858

[74] Moustogiannis, A.; Philippou, A.; Taso, O.; Zevolis, E.; Pappa, M.; Chatzigeorgiou, A.; Koutsilieris, M. The effects of muscle cell aging on myogenesis. *Int. J. Mol. Sci.,* **2021**, *22*(7), 3721. http://dx.doi.org/10.3390/ijms22073721 PMID: 33918414

[75] Yang, Y.; Yang, J.; Liu, R.; Li, H.; Luo, X.; Yang, G. Accumulation of β-catenin by lithium chloride in porcine myoblast cultures accelerates cell differentiation. *Mol. Biol. Rep.,* **2011**, *38*(3), 2043-2049. http://dx.doi.org/10.1007/s11033-010-0328-3 PMID: 20857211

[76] Pansters, N.A.M.; van der Velden, J.L.J.; Kelders, M.C.J.M.; Laeremans, H.; Schols, A.M.W.J.; Langen, R.C.J. Segregation of myoblast fusion and muscle-specific gene expression by distinct ligand-dependent inactivation of GSK-3β. *Cell. Mol. Life Sci.,* **2011**, *68*(3), 523-535. http://dx.doi.org/10.1007/s00018-010-0467-7 PMID: 20694829

[77] van der Velden, J.L.J.; Schols, A.M.W.J.; Willems, J.; Kelders, M.C.J.M.; Langen, R.C.J. Glycogen synthase kinase 3 suppresses myogenic differentiation through negative regulation of NFATc3. *J. Biol. Chem.,* **2008**, *283*(1), 358-366. http://dx.doi.org/10.1074/jbc.M707812200 PMID: 17977834

[78] Pansters, N.A.M.; Schols, A.M.W.J.; Verhees, K.J.P.; de Theije, C.C.; Snepvangers, F.J.; Kelders, M.C.J.M.; Ubags, N.D.J.; Haegens, A.; Langen, R.C.J. Muscle-specific GSK-3β ablation accelerates regeneration of disuse-atrophied skeletal muscle. *Biochim. Biophys. Acta Mol. Basis Dis.,* **2015**, *1852*(3), 490-506. http://dx.doi.org/10.1016/j.bbadis.2014.12.006 PMID: 25496993

[79] Whitley, K.C.; Watson, C.J.F.; Baranowski, R.W.; Qiu, L.; MacNeil, A.J.; Fajardo, V.A. Low dose lithium supplementation reduces muscle inflammation and serum creatine kinase in mdx mice. *Appl. Physiol. Nutr. Metab.,* **2019**, *44*, S117.

[80] Schiaffino, S.; Reggiani, C. Fiber types in mammalian skeletal muscles. *Physiol. Rev.,* **2011**, *91*(4), 1447-1531. http://dx.doi.org/10.1152/physrev.00031.2010 PMID: 22013216

[81] Barrientos, G.; Alves, J.; Toro, V.; Robles, M.C.; Muñoz, D.; Maynar, M. Association between trace elements and body composition parameters in endurance runners. *Int. J. Environ. Res. Public Health,* **2020**, *17*(18), 6563. http://dx.doi.org/10.3390/ijerph17186563 PMID: 32916939

[82] Bauer, J.; Morley, J.E.; Schols, A.M.W.J.; Ferrucci, L.; Cruz-Jentoft, A.J.; Dent, E.; Baracos, V.E.; Crawford, J.A.; Doehner, W.; Heymsfield, S.B.; Jatoi, A.; Kalantar-Zadeh, K.; Lainscak, M.; Landi, F.; Laviano, A.; Mancuso, M.; Muscaritoli, M.; Prado, C.M.; Strasser, F.; Haehling, S.; Coats, A.J.S.; Anker, S.D. Sarcopenia: A time for action. An SCWD position paper. *J. Cachexia Sarcopenia Muscle,* **2019**, *10*(5), 956-961. http://dx.doi.org/10.1002/jcsm.12483 PMID: 31523937

[83] Dhillon, R.J.S.; Hasni, S. Pathogenesis and management of sarcopenia. *Clin. Geriatr. Med.,* **2017**, *33*(1), 17-26. http://dx.doi.org/10.1016/j.cger.2016.08.002 PMID: 27886695

[84] Pagnotti, G.M.; Styner, M.; Uzer, G.; Patel, V.S.; Wright, L.E.; Ness, K.K.; Guise, T.A.; Rubin, J.; Rubin, C.T. Combating osteoporosis and obesity with exercise: leveraging cell mechanosensitivity. *Nat. Rev. Endocrinol.,* **2019**, *15*(6), 339-355. http://dx.doi.org/10.1038/s41574-019-0170-1 PMID: 30814687

[85] Manolagas, S.C. Wnt signaling and osteoporosis. *Maturitas,* **2014**, *78*(3), 233-237. http://dx.doi.org/10.1016/j.maturitas.2014.04.013 PMID: 24815296

[86] Camera, D.M.; Smiles, W.J.; Hawley, J.A. Exercise-induced skeletal muscle signaling pathways and human athletic performance. *Free Radic. Biol. Med.,* **2016**, *98*, 131-143. http://dx.doi.org/10.1016/j.freeradbiomed.2016.02.007 PMID: 26876650

[87] Lang, T.; Streeper, T.; Cawthon, P.; Baldwin, K.; Taaffe, D.R.; Harris, T.B. Sarcopenia: etiology, clinical consequences, intervention, and assessment. *Osteoporos. Int.,* **2010**, *21*(4), 543-559. http://dx.doi.org/10.1007/s00198-009-1059-y PMID: 19779761

[88] Bridge, A.D.; Brown, J.; Snider, H.; Ward, W.E.; Roy, B.D.; Josse, A.R. Consumption of Greek yogurt during 12 weeks of high-impact loading exercise increases bone formation in young, adult males – a secondary analysis from a randomized trial. *Appl. Physiol. Nutr. Metab.,* **2020**, *45*(1), 91-100. http://dx.doi.org/10.1139/apnm-2019-0396 PMID: 31652407

[89] Bridge, A.; Brown, J.; Snider, H.; Nasato, M.; Ward, W.E.; Roy, B.D.; Josse, A.R. Greek yogurt and 12 weeks of exercise training on strength, muscle thickness and body composition in lean, untrained, university-aged males. *Front. Nutr.,* **2019**, *6*, 55. http://dx.doi.org/10.3389/fnut.2019.00055 PMID: 31114790

[90] Nabrzyski, M.; Gajewska, R. Content of strontium, lithium and calcium in selected milk products and in some marine smoked fish. *Food/Nahrung,* **2002**, *46*(3), 204-208.

[91] Baranowski, R.W.; Skelly, L.E.; Josse, A.R.; Fajardo, V.A. Exploring the effects of Greek yogurt supplementation and exercise training on serum lithium and its relationship with musculoskeletal outcomes in men. *Front. Nutr.,* **2021**, *8*, 798036. http://dx.doi.org/10.3389/fnut.2021.798036 PMID: 35004824

[92] Yap, C.Y.F.; Aw, T.C. Bone Turnover Markers. *Proceedings of Singapore Healthcare,* **2010**, *19*(3), 273-275. http://dx.doi.org/10.1177/201010581001900315

[93] Conway, B.; Rene, A. Obesity as a disease: No lightweight matter. *Obes. Rev.,* **2004**, *5*(3), 145-151. http://dx.doi.org/10.1111/j.1467-789X.2004.00144.x PMID: 15245383

[94] Blüher, M. Obesity: global epidemiology and pathogenesis. *Nat. Rev. Endocrinol.,* **2019**, *15*(5), 288-298. http://dx.doi.org/10.1038/s41574-019-0176-8 PMID: 30814686

[95] Pandey, A.; Chawla, S.; Guchhait, P. Type-2 diabetes: Current understanding and future perspectives. *IUBMB Life,* **2015**, *67*(7), 506-513. http://dx.doi.org/10.1002/iub.1396 PMID: 26177573

[96] Yang, J.S.; Lu, C.C.; Kuo, S.C.; Hsu, Y.M.; Tsai, S.C.; Chen, S.Y.; Chen, Y.T.; Lin, Y.J.; Huang, Y.C.; Chen, C.J.; Lin, W.D.; Liao, W.L.; Lin, W.Y.; Liu, Y.H.; Sheu, J.C.; Tsai, F.J. Autophagy and its link to type II diabetes mellitus. *Biomedicine (Taipei),* **2017**, *7*(2), 8. http://dx.doi.org/10.1051/bmdcn/2017070201 PMID: 28612706

[97] Peselow, E.D.; Dunner, D.L.; Fieve, R.R.; Lautin, A. Lithium carbonate and weight gain. *J. Affect. Disord.,* **1980**, *2*(4), 303-310. http://dx.doi.org/10.1016/0165-0327(80)90031-2 PMID: 6450789

[98] Mangge, H.; Bengesser, S.; Dalkner, N.; Birner, A.; Fellendorf, F.; Platzer, M.; Queissner, R.; Pilz, R.; Maget, A.; Reininghaus, B.; Hamm, C.; Bauer, K.; Rieger, A.; Zelzer, S.; Fuchs, D.; Reininghaus, E. Weight gain during treatment of bipolar disorder (BD)-facts and therapeutic options. *Front. Nutr.,* **2019**, *6*, 76. http://dx.doi.org/10.3389/fnut.2019.00076 PMID: 31245376

[99] Jung, S.; Koh, J.; Kim, S.; Kim, K. Effect of lithium on the mechanism of glucose transport in skeletal muscles. *J. Nutr. Sci. Vitaminol. (Tokyo),* **2017**, *63*(6), 365-371. http://dx.doi.org/10.3177/jnsv.63.365 PMID: 29332897

[100] Gamu, D.; Juracic, E.S.; Fajardo, V.A.; Rietze, B.A.; Tran, K.; Bombardier, E.; Tupling, A.R. Phospholamban deficiency does not alter skeletal muscle SERCA pumping efficiency or predispose mice to diet-induced obesity. *Am. J. Physiol. Endocrinol. Metab.,* **2019**, *316*(3), E432-E442. http://dx.doi.org/10.1152/ajpendo.00288.2018 PMID: 30601702

[101] Lowell, B.B.; Spiegelman, B.M. Towards a molecular understanding of adaptive thermogenesis. *Nature,* **2000**, *404*(6778), 652-660. http://dx.doi.org/10.1038/35007527 PMID: 10766252

[102] Gamu, D.; Juracic, E.S.; Hall, K.J.; Tupling, A.R. The sarcoplasmic reticulum and SERCA: a nexus for muscular adaptive thermogenesis. *Appl. Physiol. Nutr. Metab.,* **2020**, *45*(1), 1-10. http://dx.doi.org/10.1139/apnm-2019-0067 PMID: 31116956

[103] Gamu, D.; Bombardier, E.; Smith, I.C.; Fajardo, V.A.; Tupling, A.R. Sarcolipin provides a novel muscle-based mechanism for adaptive thermogenesis. *Exerc. Sport Sci. Rev.,* **2014**, *42*(3), 136-142. http://dx.doi.org/10.1249/JES.0000000000000016 PMID: 24949847

[104] Fuller-Jackson, J.P.; Henry, B.A. Adipose and skeletal muscle thermogenesis: studies from large animals. *J. Endocrinol.,* **2018**, *237*(3), R99-R115. http://dx.doi.org/10.1530/JOE-18-0090 PMID: 29703782

[105] Bal, N.C.; Maurya, S.K.; Sopariwala, D.H.; Sahoo, S.K.; Gupta, S.C.; Shaikh, S.A.; Pant, M.; Rowland, L.A.; Bombardier, E.; Goonasekera, S.A.; Tupling, A.R.; Molkentin, J.D.; Periasamy, M. Sarcolipin is a newly identified regulator of muscle-based thermogenesis in mammals. *Nat. Med.,* **2012**, *18*(10), 1575-1579. http://dx.doi.org/10.1038/nm.2897 PMID: 22961106

[106] Bombardier, E.; Smith, I.C.; Gamu, D.; Fajardo, V.A.; Vigna, C.; Sayer, R.A.; Gupta, S.C.; Bal, N.C.; Periasamy, M.; Tupling, A.R. Sarcolipin trumps β‐adrenergic receptor signaling as the favored mechanism for muscle‐based diet‐induced thermogenesis. *FASEB J.,* **2013**, *27*(9), 3871-3878. http://dx.doi.org/10.1096/fj.13-230631 PMID: 23752204

[107] Bombardier, E.; Smith, I.C.; Vigna, C.; Fajardo, V.A.; Tupling, A.R. Ablation of sarcolipin decreases the energy requirements for Ca^{2+} transport by sarco(endo)plasmic reticulum Ca^{2+} -ATPases in resting skeletal muscle. *FEBS Lett.,* **2013**, *587*(11), 1687-1692. http://dx.doi.org/10.1016/j.febslet.2013.04.019 PMID: 23628781

[108] Fajardo, V.A.; Bombardier, E.; Irvine, T.; Metherel, A.H.; Stark, K.D.; Duhamel, T.; Rush, J.W.E.; Green, H.J.; Tupling, A.R. Dietary docosahexaenoic acid supplementation reduces SERCA Ca2+ transport efficiency in rat skeletal muscle. *Chem. Phys. Lipids,* **2015**, *187*, 56-61. http://dx.doi.org/10.1016/j.chemphyslip.2015.03.001 PMID: 25772907

[109] Funai, K.; Lodhi, I.J.; Spears, L.D.; Yin, L.; Song, H.; Klein, S.; Semenkovich, C.F. Skeletal muscle phospholipid metabolism regulates insulin sensitivity and contractile function. *Diabetes,* **2016**, *65*(2), 358-370. http://dx.doi.org/10.2337/db15-0659 PMID: 26512026

[110] Braun, J.L.; Teng, A.C.T.; Geromella, M.S.; Ryan, C.R.; Fenech, R.K.; MacPherson, R.E.K.; Gramolini, A.O.; Fajardo, V.A. Neuronatin promotes SERCA uncoupling and its expression is altered in skeletal muscles of high‐fat diet‐fed mice. *FEBS Lett.,* **2021**, *595*(22), 2756-2767. http://dx.doi.org/10.1002/1873-3468.14213 PMID: 34693525

[111] Nedergaard, J.; Cannon, B. The browning of white adipose tissue: some burning issues. *Cell Metab.,* **2014**, *20*(3), 396-407. http://dx.doi.org/10.1016/j.cmet.2014.07.005 PMID: 25127354

[112] Damjanov, I.; Perry, A.M.; Perry, K. *Pathology for the Health Professions-E-Book*; Elsevier Health Sciences, **2021**.

[113] Saltiel, A.R.; Pessin, J.E. Insulin signaling pathways in time and space. *Trends Cell Biol.,* **2002**, *12*(2), 65-71. http://dx.doi.org/10.1016/S0962-8924(01)02207-3 PMID: 11849969

[114] Cheng, K.; Creacy, S.; Larner, J. Insulin-like effects of lithium ion on isolated rat adipocytes I. Stimulation of glycogenesis beyond glucose transport. *Mol. Cell. Biochem.,* **1983**, *56*(2), 177-182. http://dx.doi.org/10.1007/BF00227218 PMID: 6646115

[115] Macko, A.R.; Beneze, A.N.; Teachey, M.K.; Henriksen, E.J. Roles of insulin signalling and p38 MAPK in the activation by lithium of glucose transport in insulin-resistant rat skeletal muscle. *Arch. Physiol. Biochem.,* **2008**, *114*(5), 331-339. http://dx.doi.org/10.1080/13813450802536067 PMID: 19023684

[116] Rodriguezgil, J.E.; Guinovart, J.J.; Bosch, F. Lithium restores glycogen synthesis from glucose in hepatocytes from diabetic rats. *Arch. Biochem. Biophys.,* **1993**, *301*(2), 411-415. http://dx.doi.org/10.1006/abbi.1993.1164 PMID: 8460950

[117] van der Velde, C.D.; Gordon, M.W. Manic-depressive illness, diabetes mellitus, and lithium carbonate. *Arch. Gen. Psychiatry,* **1969**, *21*(4), 478-485. http://dx.doi.org/10.1001/archpsyc.1969.01740220094011 PMID: 5807757

[118] Vendsborg, P.B.; Rafaelsen, O.J. Lithium in man: Effect on glucose tolerance and serum electrolytes. *Acta Psychiatr. Scand.,* **1973**, *49*(5), 601-610. http://dx.doi.org/10.1111/j.1600-0447.1973.tb04451.x PMID: 4760957

[119] Mellerup, E.T.; Plenge, P.; Vendsborg, P.; Rafaelsen, O.J.; Kjeldsen, H.; Agerbæk, H. Antidiabetic effects of lithium. *Lancet,* **1972**, *300*(7791), 1367-1368. http://dx.doi.org/10.1016/S0140-6736(72)92811-5 PMID: 4118232

[120] Okosieme, O.E.; Campbell, A.; Patton, K.; Evans, M.L. Transient diabetes associated with withdrawal of lithium therapy. *Diabetes Care,* **2006**, *29*(5), 1181. http://dx.doi.org/10.2337/dc06-0291 PMID: 16644668

[121] Rossetti, L. Normalization of insulin sensitivity with lithium in diabetic rats. *Diabetes,* **1989**, *38*(5), 648-652. http://dx.doi.org/10.2337/diab.38.5.648 PMID: 2653936

[122] Liberman, Z.; Eldar-Finkelman, H. Serine 332 phosphorylation of insulin receptor substrate-1 by glycogen synthase kinase-3 attenuates insulin signaling. *J. Biol. Chem.,* **2005**, *280*(6), 4422-4428. http://dx.doi.org/10.1074/jbc.M410610200 PMID: 15574412

[123] Whitley, K.C.; Hamstra, S.I.; Baranowski, R.W.; Watson, C.J.F.; MacPherson, R.E.K.; MacNeil, A.J.; Roy, B.D.; Vandenboom, R.; Fajardo, V.A. GSK3 inhibition with low dose lithium supplementation augments murine muscle fatigue resistance and specific force production. *Physiol. Rep.,* **2020**, *8*(14), e14517. http://dx.doi.org/10.14814/phy2.14517 PMID: 32729236

[124] Zhang, J.; Anshul, F.; Malhotra, D.K.; Jaume, J.; Dworkin, L.D.; Gong, R. Microdose lithium protects against pancreatic islet destruction and renal impairment in streptozotocin-elicited diabetes. *Antioxidants,* **2021**, *10*(1), 138. http://dx.doi.org/10.3390/antiox10010138 PMID: 33478120

[125] Ostrovskaya, R.U.; Ivanov, S.V.; Durnev, A.D. Neuroprotective lithium salts protect pancreatic β-cells from damage. *Bull. Exp. Biol. Med.,* **2018**, *165*(6), 758-762. http://dx.doi.org/10.1007/s10517-018-4259-7 PMID: 30353339

[126] Qiu, C.; Fratiglioni, L. Aging without dementia is achievable: Current evidence from epidemiological research. *J. Alzheimers Dis.,* **2018**, *62*(3), 933-942. http://dx.doi.org/10.3233/JAD-171037 PMID: 29562544

[127] Fan, L.; Mao, C.; Hu, X.; Zhang, S.; Yang, Z.; Hu, Z.; Sun, H.; Fan, Y.; Dong, Y.; Yang, J.; Shi, C.; Xu, Y. New insights into the pathogenesis of Alzheimer's disease. *Front. Neurol.,* **2020**, *10*, 1312. http://dx.doi.org/10.3389/fneur.2019.01312 PMID: 31998208

[128] Stutzmann, G.E. The pathogenesis of Alzheimers disease is it a lifelong "calciumopathy"? *Neuroscientist,* **2007**, *13*(5), 546-559. http://dx.doi.org/10.1177/1073858407299730 PMID: 17901262

[129] Sengoku, R. Aging and Alzheimer's disease pathology. *Neuropathology,* **2020**, *40*(1), 22-29. http://dx.doi.org/10.1111/neup.12626 PMID: 31863504

[130] Nunes, P.V.; Forlenza, O.V.; Gattaz, W.F. Lithium and risk for Alzheimer's disease in elderly patients with bipolar disorder. *Br. J. Psychiatry,* **2007**, *190*(4), 359-360. http://dx.doi.org/10.1192/bjp.bp.106.029868 PMID: 17401045

[131] Kessing, L.V.; Forman, J.L.; Andersen, P.K. Does lithium protect against dementia? *Bipolar Disord.,* **2010**, *12*(1), 87-94. http://dx.doi.org/10.1111/j.1399-5618.2009.00788.x PMID: 20148870

[132] Kessing, L.V.; Søndergård, L.; Forman, J.L.; Andersen, P.K. Lithium treatment and risk of dementia. *Arch. Gen. Psychiatry,* **2008**, *65*(11), 1331-1335. http://dx.doi.org/10.1001/archpsyc.65.11.1331 PMID: 18981345

[133] Forlenza, O.V.; De-Paula, V.J.R.; Diniz, B.S.O. Neuroprotective effects of lithium: Implications for the treatment of Alzheimer's disease and related neurodegenerative disorders. *ACS Chem. Neurosci.,* **2014**, *5*(6), 443-450. http://dx.doi.org/10.1021/cn5000309 PMID: 24766396

[134] Kerr, F.; Bjedov, I.; Sofola-Adesakin, O. Molecular mechanisms of lithium action: Switching the light on multiple targets for dementia using animal models. *Front. Mol. Neurosci.,* **2018**, *11*, 297. http://dx.doi.org/10.3389/fnmol.2018.00297 PMID: 30210290

[135] Yu, F.; Zhang, Y.; Chuang, D.M. Lithium reduces BACE1 overexpression, β amyloid accumulation, and spatial learning deficits in mice with traumatic brain injury. *J. Neurotrauma,* **2012**, *29*(13), 2342-2351. http://dx.doi.org/10.1089/neu.2012.2449 PMID: 22583494

[136] Wilson, E.N.; Do Carmo, S.; Iulita, M.F.; Hall, H.; Ducatenzeiler, A.; Marks, A.R.; Allard, S.; Jia, D.T.; Windheim, J.; Cuello, A.C. BACE1 inhibition by microdose lithium formulation NP03 rescues memory loss and early stage amyloid neuropathology. *Transl. Psychiatry,* **2017**, *7*(8), e1190. http://dx.doi.org/10.1038/tp.2017.169 PMID: 28763060

[137] Wei, Y.; Zhou, J.; Wu, J.; Huang, J. ERβ promotes Aβ degradation *via* the modulation of autophagy. *Cell Death Dis.,* **2019**, *10*(8), 565. http://dx.doi.org/10.1038/s41419-019-1786-8 PMID: 31332160

[138] Jayaraman, A.; Pike, C.J. Alzheimer's disease and type 2 diabetes: multiple mechanisms contribute to interactions. *Curr. Diab. Rep.,* **2014**, *14*(4), 476-476. http://dx.doi.org/10.1007/s11892-014-0476-2 PMID: 24526623

[139] Leszek, J.; Trypka, E.; Tarasov, V.; Ashraf, G.; Aliev, G. Type 3 Diabetes Mellitus: A novel implication of Alzheimers Disease. *Curr. Top. Med. Chem.,* **2017**, *17*(12), 1331-1335. http://dx.doi.org/10.2174/1568026617666170103163403 PMID: 28049395

[140] Forlenza, O.V.; Coutinho, A.M.N.; Aprahamian, I.; Prando, S.; Mendes, L.L.; Diniz, B.S.; Gattaz, W.F.; Buchpiguel, C.A. Long-term lithium treatment reduces glucose metabolism in the cerebellum and hippocampus of nondemented older adults: an [^{18}F]FDG-PET study. *ACS Chem. Neurosci.,* **2014**, *5*(6), 484-489. http://dx.doi.org/10.1021/cn5000315 PMID: 24730717

[141] Kohno, T.; Shiga, T.; Toyomaki, A.; Kusumi, I.; Matsuyama, T.; Inoue, T.; Katoh, C.; Koyama, T.; Tamaki, N. Effects of lithium on brain glucose metabolism in healthy men. *J. Clin. Psychopharmacol.,* **2007**, *27*(6), 698-702. http://dx.doi.org/10.1097/jcp.0b013e31815a23c2 PMID: 18004140

[142] Nunes, M.A.; Viel, T.A.; Buck, H.S. Microdose lithium treatment stabilized cognitive impairment in patients with Alzheimer's disease. *Curr. Alzheimer Res.,* **2013**, *10*(1), 104-107. PMID: 22746245

[143] Wilson, E.N.; Do Carmo, S.; Welikovitch, L.A.; Hall, H.; Aguilar, L.F.; Foret, M.K.; Iulita, M.F.; Jia, D.T.; Marks, A.R.; Allard, S.; Emmerson, J.T.; Ducatenzeiler, A.; Cuello, A.C. NP03, a Microdose lithium formulation, blunts early amyloid post-plaque neuropathology in McGill-R-Thy1-APP Alzheimer-like transgenic rats. *J. Alzheimers Dis.,* **2020**, *73*(2), 723-739. http://dx.doi.org/10.3233/JAD-190862 PMID: 31868669

[144] Kessing, L.V.; Gerds, T.A.; Knudsen, N.N.; Jørgensen, L.F.; Kristiansen, S.M.; Voutchkova, D.; Ernstsen, V.; Schullehner, J.; Hansen, B.; Andersen, P.K.; Ersbøll, A.K. Association of lithium in drinking water with the incidence of dementia. *JAMA Psychiatry,* **2017**, *74*(10), 1005-1010. http://dx.doi.org/10.1001/jamapsychiatry.2017.2362 PMID: 28832877

[145] Parker, W.F.; Gorges, R.J.; Gao, Y.N.; Zhang, Y.; Hur, K.; Gibbons, R.D. Association between groundwater lithium and the diagnosis of bipolar disorder and dementia in the united states. *JAMA Psychiatry,* **2018**, *75*(7), 751-754. http://dx.doi.org/10.1001/jamapsychiatry.2018.1020 PMID: 29799907

[146] Nunes, M.A.; Schöwe, N.M.; Monteiro-Silva, K.C.; Baraldi-Tornisielo, T.; Souza, S.I.G.; Balthazar, J.; Albuquerque, M.S.; Caetano, A.L.; Viel, T.A.; Buck, H.S. Chronic microdose lithium treatment prevented memory loss and neurohistopathological changes in a transgenic mouse model of Alzheimer's disease. *PLoS One,* **2015**, *10*(11), e0142267. http://dx.doi.org/10.1371/journal.pone.0142267 PMID: 26605788

[147] Pouladi, M.A.; Brillaud, E.; Xie, Y.; Conforti, P.; Graham, R.K.; Ehrnhoefer, D.E.; Franciosi, S.; Zhang, W.; Poucheret, P.; Compte, E.; Maurel, J.C.; Zuccato, C.; Cattaneo, E.; Néri, C.; Hayden, M.R. NP03, a novel low-dose lithium formulation, is neuroprotective in the YAC128 mouse model of Huntington disease. *Neurobiol. Dis.,* **2012**, *48*(3), 282-289. http://dx.doi.org/10.1016/j.nbd.2012.06.026 PMID: 22796360

[148] Radak, Z.; Hart, N.; Sarga, L.; Koltai, E.; Atalay, M.; Ohno, H.; Boldogh, I. Exercise plays a preventive role against Alzheimer's disease. *J. Alzheimers Dis.,* **2010**, *20*(3), 777-783. http://dx.doi.org/10.3233/JAD-2010-091531 PMID: 20182027

[149] Intlekofer, K.A.; Cotman, C.W. Exercise counteracts declining hippocampal function in aging and Alzheimer's disease. *Neurobiol. Dis.,* **2013**, *57*, 47-55. http://dx.doi.org/10.1016/j.nbd.2012.06.011 PMID: 22750524

[150] Baranowski, B.J.; Marko, D.M.; Fenech, R.K.; Yang, A.J.T.; MacPherson, R.E.K. Healthy brain, healthy life: A review of diet and exercise interventions to promote brain health and reduce Alzheimer's disease risk. *Appl. Physiol. Nutr. Metab.,* **2020**, *45*(10), 1055-1065. http://dx.doi.org/10.1139/apnm-2019-0910 PMID: 32717151

[151] Jeong, J.H.; Koo, J.H.; Cho, J.Y.; Kang, E.B. Neuroprotective effect of treadmill exercise against blunted brain insulin signaling, NADPH oxidase, and Tau hyperphosphorylation in rats fed a high-fat diet. *Brain Res. Bull.,* **2018**, *142*, 374-383. http://dx.doi.org/10.1016/j.brainresbull.2018.08.001 PMID: 30081082

[152] Ruegsegger, G.N.; Vanderboom, P.M.; Dasari, S.; Klaus, K.A.; Kabiraj, P.; McCarthy, C.B.; Lucchinetti, C.F.; Nair, K.S. Exercise and metformin counteract altered mitochondrial function in the insulin-resistant brain. *JCI Insight,* **2019**, *4*(18), e130681. http://dx.doi.org/10.1172/jci.insight.130681 PMID: 31534057

[153] Park, J.; Cheon, W.; Kim, K. Effects of long-term endurance exercise and lithium treatment on neuroprotective factors in hippocampus of obese rats. *Int. J. Environ. Res. Public Health,* **2020**, *17*(9), 3317. http://dx.doi.org/10.3390/ijerph17093317 PMID: 32397675

[154] Salminen, A.; Kaarniranta, K.; Kauppinen, A. Regulation of longevity by FGF21: Interaction between energy metabolism and stress responses. *Ageing Res. Rev.,* **2017**, *37*, 79-93. http://dx.doi.org/10.1016/j.arr.2017.05.004 PMID: 28552719

[155] Nassar, A.; Azab, A.N. Effects of lithium on inflammation. *ACS Chem. Neurosci.,* **2014**, *5*(6), 451-458. http://dx.doi.org/10.1021/cn500038f PMID: 24803181

[156] Khairova, R.; Pawar, R.; Salvadore, G.; Juruena, M.F.; de Sousa, R.T.; Soeiro-de-Souza, M.G.; Salvador, M.; Zarate, C.A.; Gattaz, W.F.; Machado-Vieira, R. Effects of lithium on oxidative stress parameters in healthy subjects. *Mol. Med. Rep.,* **2012**, *5*(3), 680-682. PMID: 22200861

[157] Franceschi, C.; Garagnani, P.; Vitale, G.; Capri, M.; Salvioli, S. Inflammaging and 'Garb-aging'. *Trends Endocrinol. Metab.,* **2017**, *28*(3), 199-212. http://dx.doi.org/10.1016/j.tem.2016.09.005 PMID: 27789101

[158] Franceschi, C.; Campisi, J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *J. Gerontol. A Biol. Sci. Med. Sci.,* **2014**, *69*(Suppl. 1), S4-S9. http://dx.doi.org/10.1093/gerona/glu057 PMID: 24833586

[159] Mau, T.; Yung, R. Adipose tissue inflammation in aging. *Exp. Gerontol.,* **2018**, *105*, 27-31. http://dx.doi.org/10.1016/j.exger.2017.10.014 PMID: 29054535

[160] van Deursen, J.M. The role of senescent cells in ageing. *Nature,* **2014**, *509*(7501), 439-446. http://dx.doi.org/10.1038/nature13193 PMID: 24848057

[161] Olivieri, F.; Prattichizzo, F.; Grillari, J.; Balistreri, C.R. Cellular senescence and inflammaging in age-related diseases. *Mediators Inflamm.,* **2018**, *2018*, 1-6. http://dx.doi.org/10.1155/2018/9076485 PMID: 29849499

[162] Schmeer, C.; Kretz, A.; Wengerodt, D.; Stojiljkovic, M.; Witte, O.W. Dissecting aging and senescence-current concepts and open lessons. *Cells,* **2019**, *8*(11), 1446. http://dx.doi.org/10.3390/cells8111446 PMID: 31731770

[163] Martin, M.; Rehani, K.; Jope, R.S.; Michalek, S.M. Toll-like receptor–mediated cytokine production is differentially regulated by glycogen synthase kinase 3. *Nat. Immunol.,* **2005**, *6*(8), 777-784. http://dx.doi.org/10.1038/ni1221 PMID: 16007092

[164] Viel, T.; Chinta, S.; Rane, A.; Chamoli, M.; Buck, H.; Andersen, J. Microdose lithium reduces cellular senescence in human astrocytes

- a potential pharmacotherapy for COVID-19? *Aging (Albany NY),* **2020**, *12*(11), 10035-10040.
http://dx.doi.org/10.18632/aging.103449 PMID: 32534451

[165] Weidinger, A.; Kozlov, A. Biological activities of reactive oxygen and nitrogen species: Oxidative stress *versus* signal transduction. *Biomolecules,* **2015**, *5*(2), 472-484.
http://dx.doi.org/10.3390/biom5020472 PMID: 25884116

[166] Machado-Vieira, R.; Andreazza, A.C.; Viale, C.I.; Zanatto, V.; Cereser, V., Jr; Vargas, R.S.; Kapczinski, F.; Portela, L.V.; Souza, D.O.; Salvador, M.; Gentil, V. Oxidative stress parameters in unmedicated and treated bipolar subjects during initial manic episode: A possible role for lithium antioxidant effects. *Neurosci. Lett.,* **2007**, *421*(1), 33-36.
http://dx.doi.org/10.1016/j.neulet.2007.05.016 PMID: 17548157

[167] Lundberg, M.; Millischer, V.; Backlund, L.; Martinsson, L.; Stenvinkel, P.; Sellgren, C.M.; Lavebratt, C.; Schalling, M. Lithium and the interplay between telomeres and mitochondria in bipolar disorder. *Front. Psychiatry,* **2020**, *11*, 586083-586083.
http://dx.doi.org/10.3389/fpsyt.2020.586083 PMID: 33132941

[168] Tam, Z.Y.; Gruber, J.; Ng, L.F.; Halliwell, B.; Gunawan, R. Effects of lithium on age-related decline in mitochondrial turnover and function in Caenorhabditis elegans. *J. Gerontol. A Biol. Sci. Med. Sci.,* **2014**, *69*(7), 810-820.
http://dx.doi.org/10.1093/gerona/glt210 PMID: 24398558

[169] Chuang, D.M.; Wang, Z.; Chiu, C.T. GSK-3 as a target for lithium-induced neuroprotection against excitotoxicity in neuronal cultures and animal models of ischemic stroke. *Front. Mol. Neurosci.,* **2011**, *4*, 15.
http://dx.doi.org/10.3389/fnmol.2011.00015 PMID: 21886605

[170] Albayrak, A.; Halici, Z.; Polat, B.; Karakus, E.; Cadirci, E.; Bayir, Y.; Kunak, S.; Karcioglu, S.S.; Yigit, S.; Unal, D.; Atamanalp, S.S. Protective effects of lithium: A new look at an old drug with potential antioxidative and anti-inflammatory effects in an animal model of sepsis. *Int. Immunopharmacol.,* **2013**, *16*(1), 35-40.
http://dx.doi.org/10.1016/j.intimp.2013.03.018 PMID: 23542012

[171] Kim, Y.H.; Rane, A.; Lussier, S.; Andersen, J.K. Lithium protects against oxidative stress-mediated cell death in α-synuclein-overexpressing *in vitro* and *in vivo* models of Parkinson's disease. *J. Neurosci. Res.,* **2011**, *89*(10), 1666-1675.
http://dx.doi.org/10.1002/jnr.22700 PMID: 21710541

[172] Shao, L.; Cui, J.; Young, L.T.; Wang, J.F. The effect of mood stabilizer lithium on expression and activity of glutathione s-transferase isoenzymes. *Neuroscience,* **2008**, *151*(2), 518-524.
http://dx.doi.org/10.1016/j.neuroscience.2007.10.041 PMID: 18082333

[173] Wang, J.F.; Shao, L.; Sun, X.; Young, L.T. Glutathione S-transferase is a novel target for mood stabilizing drugs in primary cultured neurons. *J. Neurochem.,* **2004**, *88*(6), 1477-1484.
http://dx.doi.org/10.1046/j.1471-4159.2003.02276.x PMID: 15009649

[174] Mayer, M.P.; Bukau, B. Hsp70 chaperones: Cellular functions and molecular mechanism. *Cell. Mol. Life Sci.,* **2005**, *62*(6), 670-684.
http://dx.doi.org/10.1007/s00018-004-4464-6 PMID: 15770419

[175] Fu, M.H.; Tupling, A.R. Protective effects of Hsp70 on the structure and function of SERCA2a expressed in HEK-293 cells during heat stress. *Am. J. Physiol. Heart Circ. Physiol.,* **2009**, *296*(4), H1175-H1183.
http://dx.doi.org/10.1152/ajpheart.01276.2008 PMID: 19252085

[176] Tupling, A.R.; Gramolini, A.O.; Duhamel, T.A.; Kondo, H.; Asahi, M.; Tsuchiya, S.C.; Borrelli, M.J.; Lepock, J.R.; Otsu, K.; Hori, M.; MacLennan, D.H.; Green, H.J. HSP70 binds to the fast-twitch skeletal muscle sarco(endo)plasmic reticulum Ca^{2+} -ATPase (SERCA1a) and prevents thermal inactivation. *J. Biol. Chem.,* **2004**, *279*(50), 52382-52389.
http://dx.doi.org/10.1074/jbc.M409336200 PMID: 15371420

[177] Castillo-Quan, J.I.; Li, L.; Kinghorn, K.J.; Ivanov, D.K.; Tain, L.S.; Slack, C.; Kerr, F.; Nespital, T.; Thornton, J.; Hardy, J.; Bjedov, I.; Partridge, L. Lithium promotes longevity through GSK3/NRF2-dependent hormesis. *Cell Rep.,* **2016**, *15*(3), 638-650.
http://dx.doi.org/10.1016/j.celrep.2016.03.041 PMID: 27068460

[178] Zarse, K.; Terao, T.; Tian, J.; Iwata, N.; Ishii, N.; Ristow, M. Low-dose lithium uptake promotes longevity in humans and metazoans. *Eur. J. Nutr.,* **2011**, *50*(5), 387-389.
http://dx.doi.org/10.1007/s00394-011-0171-x PMID: 21301855

[179] Calabrese, V.; Cornelius, C.; Dinkova-Kostova, A.T.; Calabrese, E.J.; Mattson, M.P. Cellular stress responses, the hormesis paradigm, and vitagenes: novel targets for therapeutic intervention in neurodegenerative disorders. *Antioxid. Redox Signal.,* **2010**, *13*(11), 1763-1811.
http://dx.doi.org/10.1089/ars.2009.3074 PMID: 20446769

[180] Calabrese, V.; Cornelius, C.; Dinkova-Kostova, A.T.; Iavicoli, I.; Di Paola, R.; Koverech, A.; Cuzzocrea, S.; Rizzarelli, E.; Calabrese, E.J. Cellular stress responses, hormetic phytochemicals and vitagenes in aging and longevity. *Biochim. Biophys. Acta Mol. Basis Dis.,* **2012**, *1822*(5), 753-783.
http://dx.doi.org/10.1016/j.bbadis.2011.11.002 PMID: 22108204

[181] Calabrese, V.; Mancuso, C.; Calvani, M.; Rizzarelli, E.; Butterfield, D.A.; Giuffrida Stella, A.M. Nitric oxide in the central nervous system: neuroprotection *versus* neurotoxicity. *Nat. Rev. Neurosci.,* **2007**, *8*(10), 766-775.
http://dx.doi.org/10.1038/nrn2214 PMID: 17882254

[182] Wang, W.Z. Investigation of reperfusion injury and ischemic preconditioning in microsurgery. *Microsurgery,* **2009**, *29*(1), 72-79.
http://dx.doi.org/10.1002/micr.20587 PMID: 18946882

[183] Liu, Z.; Gong, R. Remote ischemic preconditioning for kidney protection: GSK3β-centric insights into the mechanism of action. *Am. J. Kidney Dis.,* **2015**, *66*(5), 846-856.
http://dx.doi.org/10.1053/j.ajkd.2015.06.026 PMID: 26271146

[184] Li, Q.; Li, H.; Roughton, K.; Wang, X.; Kroemer, G.; Blomgren, K.; Zhu, C. Lithium reduces apoptosis and autophagy after neonatal hypoxia–ischemia. *Cell Death Dis.,* **2010**, *1*(7), e56-e56.
http://dx.doi.org/10.1038/cddis.2010.33 PMID: 21364661

[185] Xu, J.; Culman, J.; Blume, A.; Brecht, S.; Gohlke, P. Chronic treatment with a low dose of lithium protects the brain against ischemic injury by reducing apoptotic death. *Stroke,* **2003**, *34*(5), 1287-1292.
http://dx.doi.org/10.1161/01.STR.0000066308.25088.64 PMID: 12677021

[186] Talab, S.S.; Elmi, A.; Emami, H.; Nezami, B.G.; Assa, S.; Ghasemi, M.; Tavangar, S.M.; Dehpour, A.R. Protective effects of acute lithium preconditioning against renal ischemia/reperfusion injury in rat: Role of nitric oxide and cyclooxygenase systems. *Eur. J. Pharmacol.,* **2012**, *681*(1-3), 94-99.
http://dx.doi.org/10.1016/j.ejphar.2012.01.042 PMID: 22342279

[187] Faghihi, M.; Mirershadi, F.; Dehpour, A.R.; Bazargan, M. Preconditioning with acute and chronic lithium administration reduces ischemia/reperfusion injury mediated by cyclooxygenase not nitric oxide synthase pathway in isolated rat heart. *Eur. J. Pharmacol.,* **2008**, *597*(1-3), 57-63.
http://dx.doi.org/10.1016/j.ejphar.2008.08.010 PMID: 18789320

[188] Ren, M.; Senatorov, V.V.; Chen, R.W.; Chuang, D.M. Postinsult treatment with lithium reduces brain damage and facilitates neurological recovery in a rat ischemia/reperfusion model. *Proc. Natl. Acad. Sci. USA,* **2003**, *100*(10), 6210-6215.
http://dx.doi.org/10.1073/pnas.0937423100 PMID: 12732732

[189] Talab, S.S.; Emami, H.; Elmi, A.; Nezami, B.G.; Assa, S.; Deroee, A.F.; Daneshmand, A.; Tavangar, S.M.; Dehpour, A.R. Chronic lithium treatment protects the rat kidney against ischemia/reperfusion injury: The role of nitric oxide and cyclooxygenase pathways. *Eur. J. Pharmacol.,* **2010**, *647*(1-3), 171-177.
http://dx.doi.org/10.1016/j.ejphar.2010.08.036 PMID: 20826134

[190] Liu, A.; Fang, H.; Dahmen, U.; Dirsch, O. Chronic lithium treatment protects against liver ischemia/reperfusion injury in rats. *Liver Transpl.,* **2013**, *19*(7), 762-772.
http://dx.doi.org/10.1002/lt.23666 PMID: 23696274