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Mechanism of therapeutic action of abiogenic Li^+ and Ga^{3+} ions: insights from theoretical studies

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Lithium and gallium (Li^+ and Ga^{3+}) exhibit no known biological functions and are categorized as abiogenic ions. However, they are used in medicine (in the form of soluble salts) as a first-line drugs for treatment of bipolar disorder (Li^+) or cancer-related hypercalcemia (Ga^{3+}) as well as a drug with antiproliferative action in clinical trials (Ga^{3+}). Even though their therapeutic effects are well known, there are many unanswered questions concerning their mechanism of action. The main hypotheses posit competition between Li^+ and the native Mg^{2+}, and between Ga^{3+} and the cognate Fe^{3+} ions for binding to some metalloenzymes involved in cell signaling and cell proliferation, respectively. The conducted theoretical research explains some of the most accepted hypotheses about the therapeutic action of the two alien cations. The factors governing the competition between biogenic and abiogenic cations in protein binding sites are also revealed. The theoretical results are in line with experimental data.

Keywords: lithium, gallium, mechanism of action, theoretical study.

INTRODUCTION

Since the beginning of time mankind has struggled not only to understand the laws of nature but also to apply them for the general benefit. Over the centuries, medicine and pharmacy have been prioritized areas of research/application achieving tremendous success in their development [1, 2]. Nowadays the term "drug" is usually associated with a variety of organic/peptide/polypeptide compounds from different classes of medications. Inorganic substances, however, such as metal salts or complexes, can also exert curative effect and be employed in treating health disorders.

About 40% of all known proteins contain metal cations, which appear as indispensable players in a plethora of essential tasks such as protein structure stabilization, enzyme catalysis, hormone secretion, signal transduction, blood coagulation, respiration and photosynthesis [1, 3, 4, 5]. In the course of evolution biological function has been bestowed on about two dozen metal species based on their bioavailability and chemical properties. They are known as "biogenic" or "native" ions, among which the most common are Na^+, K^+, Mg^{2+}, Ca^{2+} and Zn^{2+} and the redox-active transition metal cations $Mn^{2+/3+/4+}$, $Fe^{2+/3+}$ and $Cu^{+/2+}$ [3, 4, 5]. Other (abiogenic) metal ions, excluded from the evolutionary process, such as Hg^{2+}, Pb^{2+}, Al^{3+}, upon entering the host organism, could disrupt cellular functions by competing with some of the above-mentioned native ions thus intoxicating the recipient. On the other hand, there are a few alien metal cations (Li^+, Sr^{2+} and Ga^{3+}) with no known vital functions in humans, that exert therapeutic effects based on their similarity with some cognate metals. In this review we focus on lithium and gallium that have been an object of investigation of our group for some time. We summarize the most accepted hypotheses concerning the mechanism of action as well as the applications of Li^+ and Ga^{3+} in medicine. Using the methods of the theoretical chemistry we have tried to shed light on the suggested competition between the biogenic and alien metal ions.

MECHANISM OF ACTION

Lithium

Lithium has been applied in the form of soluble salts in concentration range of 0.6–1.2 mM to treat patients suffering from bipolar disorder [6]. This illness affects 1–3% of the world's population and

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is characterized by episodes of mania and depression separated by periods of normal behavior [6, 7]. Although the beneficiary effect of lithium therapy has been known for decades, its mechanism of action is still enigmatic. Several hypotheses have been put forward. Among them, the most accepted one posits competition between the alien Li^+ and the native Mg^{2+} and subsequent inhibition of several overexpressed enzymes involved in cell signaling, such as inositol monophosphatase (IMPase) and glycogen-synthase kinase 3β (GSK-3β) [4, 6–8]. Lihium's direct inhibition of IMPase has led to the formation of the "inositol depletion hypothesis" – by decreasing the free inositol levels, lithium dampens the activation of downstream signaling pathways in neurons [6–9]. The other enzyme of interest – GSK-3β, is a component of many signaling pathways responsible for specific neurotransmission in the brain [4, 6, 7, 9, 10]. Note, however, that other essential magnesium enzymes in the cell remain unaffected by lithium action. Furthermore, another channel of lithium's therapeutic action has been recently suggested: lithium not only competes with magnesium to bind enzymes but it can also associate with magnesium-loaded ATP to modulate the native receptor's response involved in cell signaling [10, 11].

Lithium is expected to compete mainly with magnesium due to the similarity in their physicochemical properties. The "diagonal rule" brings Li^+ closer to Mg^{2+} than to its fellow alkali metals from group IA. This is proven by the fact that both Li^+ and Mg^{2+} are "hard" nonpolarizable cations with affinity towards hard "O" – containing ligands. They also have similar ionic radii (R_{ion}) for a given coordination number (CN): $R_{ion}(Li^+)$ = 0.59 Å and $R_{ion}(Mg^{2+})$ = 0.57Å for CN = 4, and $R_{ion}(Li^+)$ = 0.76 Å and $R_{ion}(Mg^{2+})$ = 0.72 Å for a CN = 6 [12]. Still they differ in their ionic charge (+1 for Li and +2 for Mg) and hydration free energies: –123.5 kcal/mol (Li^+) and –455.5 kcal/mol (Mg^{2+}) [13]. Although there are a few experiments proving lithium's ability to compete with magnesium for binding the above-mentioned enzymes and ATP-complexes [6, 7, 9, 11], there still remain questions about the ability of Li^+ to substitute for Mg^{2+} in IMPase and GSK-3β but not in other essential Mg^{2+}-containing enzymes in the cell. Also, the exact geometry/conformation and protonation state of the active ATP-Mg-Li complex has not been known.

Gallium

The first use of gallium in medicine was as a tumor-imaging ^{67}Ga-scan which was in time replaced by the more effective PET-scan [14]. But due to its ability to concentrate especially in liver cancer cells it was investigated for antiproliferative action. As a side effect it was found that infusion of gallium nitrate reduces blood-level calcium and so it is nowadays used as Ganite™ to treat patients with cancer-related hypercalcemia [15]. However, newer gallium compounds such as gallium maltolate and *tris*(8-quinolonato)gallium(III) (KP46) have already passed the preclinical examination with promising results of their anticancer action [16–20]. Ga^{3+} could also be used in a combination with other antitumor drugs like cis-platinum or tiosemicarbazones [21, 22]. The rationale behind gallium's anticancer effect lies upon its action as an iron mimetic species [14, 19, 23, 24] and iron-competitor in tumor cells, that need iron for their fast proliferation. Sharing the same oxidation state and similar ionic radius with Fe^{3+} ($R_{ion}(Ga^{3+})$ = 0.620 Å in octahedral complexes compared with $R_{ion}(Fe^{3+})$ = 0.645 Å for high spin complexes as well as tetrahedral ionic radius 0.47 Å (Ga^{3+}) and 0.49 Å (Fe^{3+})) gallium could deceive the cell machinery and be taken up as iron. The two metal ions have also similar ionization potential and electron affinity values [5, 14]. However, while Fe^{3+} may undergo redox-reactions under physiological conditions, Ga^{3+} is redox-inactive and cannot participate in redox reactions in metalloenzymes.

Gallium's most probable target in tumor cells is the enzyme ribonucleotide reductase (RR) [5, 14, 18, 19, 24]. RR is a heterodimer which consists of two homodimeric M1 and M2 subunits. RRM1 contains a substrate (nucleotide diphosphate) and two effector-binding sites while RRM2 consists of a binuclear iron center and a tyrosil free radical. Its main purpose is the *de novo* synthesis of deoxyribonucleotides from ribonucleotides [25]. The iron center is of extreme importance because it is responsible for the generation of the radical which is later used in the redox reaction with the nucleotide-substrates. In the iron center, Fe^{2+} is oxidized to Fe^{3+}. Substituting the Fe^{3+} cation with the redox-inactive Ga^{3+} renders the enzyme inactive. Although it is a widely accepted hypothesis and there is some experimental evidence [14], the intimate mechanism of the competition between the two metal ions is poorly understood.

Another hypothesis of gallium's therapeutic action states that it may compete with iron for human transferrin (Tf), a glycoprotein, transporting Fe^{3+} in the bloodstream [26], as well as that the newly formed Tf-Ga^{3+} complex may compete with the Tf-Fe^{3+} complex for the Tf-receptor which would lead to decrease in the native ion's intracellular concentration level [5, 14, 24].

The last and newest hypothesis concerning gallium's mechanism of action coincides with the information that it is able to form complexes with different nucleotide-diphosphates [14, 26]. Since the substrates for RR are namely NDP (for example

ADP) the probable NDP-Ga^{3+} complex may directly inhibit the enzyme by blocking its substrate-binding site. This hypothesis is an object of ongoing investigation from our group.

METHODS

Models used

Interactions between the metal and ligands from its first coordination shell are electrostatic in origin and dominate the energetics of the metal loaded binding site. Thus, we modeled the first coordination sphere of the enzymes of interest as a complex with either the native or the alien cation and evaluated the thermodynamic parameters of the respective substitution reaction (see below) [4, 5, 10]. The side chains of Asp^-/Glu^-, Asn/Gln and the backbone of the peptide are modeled as acetate (CH_3COO^-), acetamide (CH_3CONH_2) and *N*-methylacetamide ($CH_3CONHCH_3$), respectively, whereas the neutral His and ionized Tyr are presented as imidazole and phenolate, respectively. The preferable coordination number of the metal ions has been taken into account. The metal-binding centers of the enzymes were modeled in accordance with the respective Protein Data Bank (PDB) X-ray structures.

Reaction modeled

The competition between the native (Mg^{2+}/Fe^{3+}) and alien (Li^+/Ga^{3+}) cations can be described by the following model reaction:

$$[\text{native ion}^{n+}\text{-protein}]+[\text{alien ion}^{m+}\text{-aq}] \rightarrow [\text{alien ion}^{m+}\text{-protein}]+[\text{native ion}^{n+}\text{-aq}] \quad (1)$$

In eq.1 [native/alien ion^{n+}-protein] and [native/alien ion^{n+}-aq] represent the metal cation bound inside the enzyme active site and outside binding cavity, respectively. The outcome of the competition between the two metal cations is assessed by the free energy evaluated in an environment characterized by a dielectric constant $\varepsilon = x$:

$$\Delta G^x = \Delta G^1 + \Delta G_{solv}{}^x([\text{alien ion}^{m+}\text{-protein}]) + \Delta G_{solv}{}^x([\text{native ion}^{n+}\text{-aq}]) - \Delta G_{solv}{}^x([\text{native ion}^{n+}\text{-protein}]) - \Delta G_{solv}{}^x([\text{alien ion}^{m+}\text{-aq}]) \quad (2)$$

A negative value implies an alien-ion selective site, while a positive one means that the abiogenic ion cannot substitute for the native metal. ΔG^1 is the gas-phase free energy for the modeled reaction, and $\Delta G_{solv}{}^x$ is the free energy for transferring a molecule from the gas phase to a medium characterized by a dielectric constant $\varepsilon = x$.

DFT/CDM calculations

All calculations in the gas phase were done using either the Gaussian 03 [27] or the Gaussian 09 [28] programs. For each study the most adequate combination of DFT functional/basis set was chosen in order to reproduce the experimental data for the known metal ion-complexes [29–31]. After the full optimization of each structure and evaluating its electronic energy (E_{elect}), vibrational frequency calculations were performed. No imaginary frequencies were found indicating that the optimized structure corresponds to a minimum in its potential energy surface. For each method/basis set the vibrational frequencies were scaled by the corresponding empirical factor [32, 33] and were used to compute the thermal energies, including the zero-point energy (E_T) and entropy (S) corrections, in line with the statistical mechanical formulas [34]. The reaction free energy in the gas phase, ΔG^1, at room temperature, $T = 298.15$ K, was calculated according to the formula:

$$\Delta G^1 = \Delta E_{elec} + \Delta E_T + \Delta PV - T\Delta S, \quad (3)$$

where ΔE_{elec}, ΔE_T, ΔPV (work term) and ΔS are the differences between the products and the reactants.

Continuum dielectric method (CDM) calculations of the optimized metal constructs were performed [4, 5, 10] mimicking buried protein cavities characterized with dielectric constant $\varepsilon = 4$, partially solvent accessible active centers with $\varepsilon = 10$, or solvent exposed binding sites with $\varepsilon \approx 30$.

RESULTS

Li^+ vs Mg^{2+} in GSK-3β and IMPase polynuclear sites

Crystallographic data indicates that GSK-3β possesses a solvent-accessible binuclear magnesium binding site (PDB entry 1PYX), where the two metals are bridged by an aspartate amino acid residue. Accordingly, the active site structure was modeled, optimized and its Li^+/Mg^{2+} selectivity assessed (Fig. 1). The calculations reveal that the binuclear binding site is vulnerable to Li^+ attack: the substitution of either of the Mg^{2+} cations by Li^+ is favorable in both buried and solvent-exposed sites (Fig. 1, negative ΔG^ε, $\varepsilon = 4$–30).

IMPase, a key trinuclear Mg^{2+} enzyme of the phosphatidylinositol signaling pathway, is another

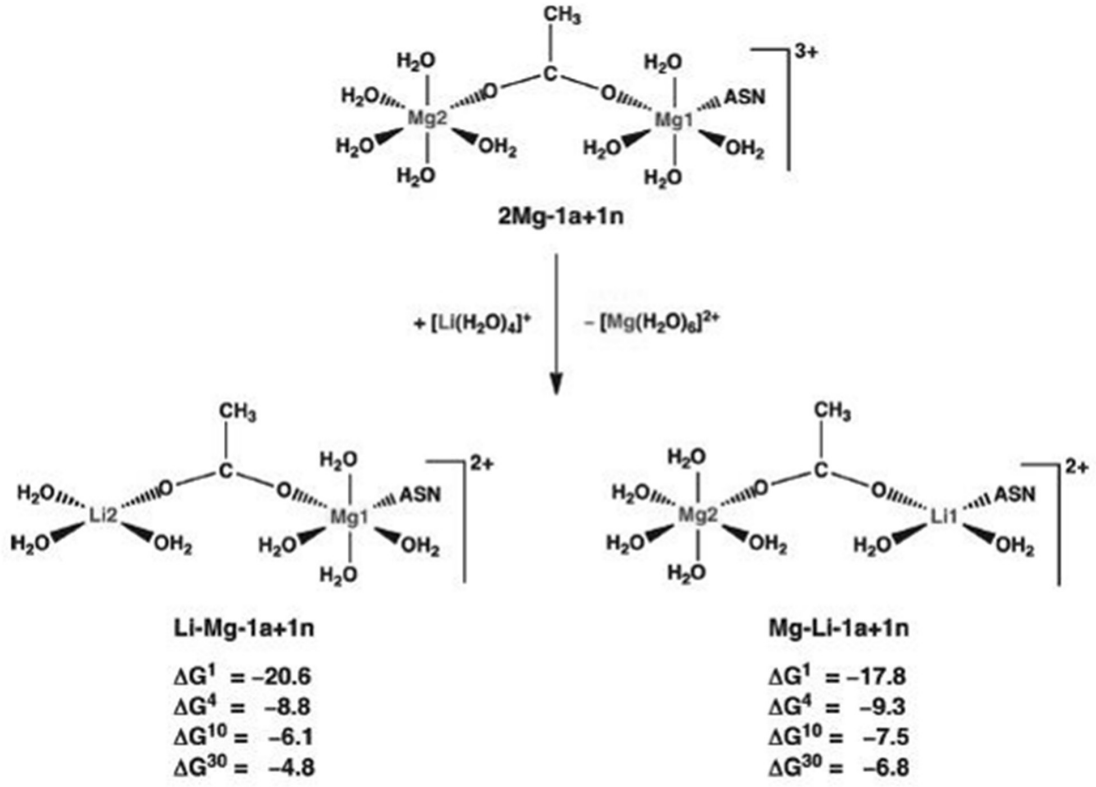

Fig. 1. Free energies, ΔG° (in kcal/mol) for $Mg^{2+} \rightarrow Li^+$ substitution in a model GSK-3β binuclear active center. Calculations are performed at B3LYP/6-31+G(3d,p) level [4].

putative target for Li^+ therapy. The calculations predict that solvent exposed binding sites 2 and 3 (Fig. 2) are prone to $Mg^{2+} \rightarrow Li^+$ substitution, evidenced by negative ΔG^{30}. Results obtained imply that displacing Mg^{2+} from binding site 2 is more thermodynamically favorable than that from binding site 3 (lower ΔG^{30} for the former than latter). These findings are in line with the experimental ^7Li NMR data which shows that, first of all, Li^+ can displace Mg^{2+} from IMPase active centers, and, second, that the site of the Li^+ attack is, indeed, center 2 [35]

The calculations answer the question why Li^+ competes successfully with Mg^{2+} in signal transducing proteins, such as GSK-3β and IMPase, but not in other essential Mg^{2+} proteins. This is because the binding sites of the former enzymes possess high *positive* charge density (complex net charge 3+ for GSK-3β and 2+ for IMPase) and are solvent-exposed, whereas the binding sites of majority of the Mg^{2+} essential enzymes have higher *negative* charge density (overall charge between –1 and +1) and are buried into the protein structure (results not shown) [4].

Li^+ in Mg^{2+}-ATP complexes

Lithium has been hypothesized to bind to Mg^{2+}-loaded adenosine triphosphate (ATP) forming a Mg^{2+}-ATP-Li^+ complex which, when protein-bound, may elicit different responses from key ATP-dependent enzymes/receptors involved in cell signaling [36]. The last hypothesis is supported by recent experiments showing that the Mg^{2+}-ATP-Li^+ complex can indeed modulate the neuronal purine receptor response [11]. The P2X receptor, a ligand-gated ion channel that mediates the influx of extracellular Ca^{2+} into the cytoplasm, exhibited prolonged activation when stimulated by Mg^{2+}-ATP-Li^+ as compared to the „native“ Mg^{2+}-ATP. Therefore, when Mg^{2+} is already bound to ATP, which phosphate(s) best accommodate Li^+ binding? Is the native Mg^{2+}-ATP conformation altered by Li^+ coordination, thus affecting enzyme/receptor recognition?

The calculations reveal how the metal cation type and its binding mode affect the ATP conformation. Li^+ bidentate binding via β and γ phosphates and OH^- metal bridge to Mg^{2+}-loaded ATP (Fig. 3) did not significantly alter the ATP conformation or

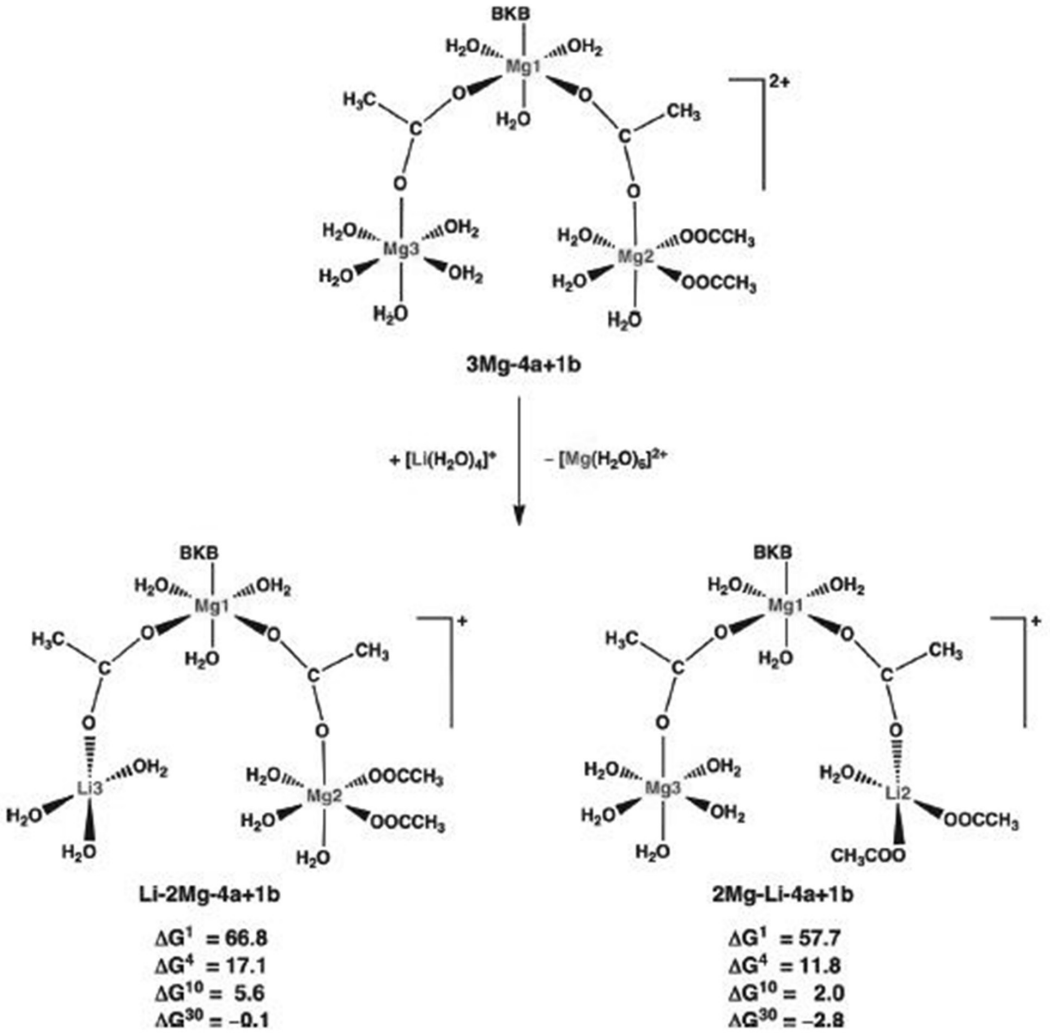

Fig. 2. Free energies, ΔG^{ε} (in kcal/mol) for $Mg^{2+} \rightarrow Li^{+}$ substitution in a model IMPase trinuclear binding site. Calculations are performed at B3LYP/6-31+G(3d,p) level [4].

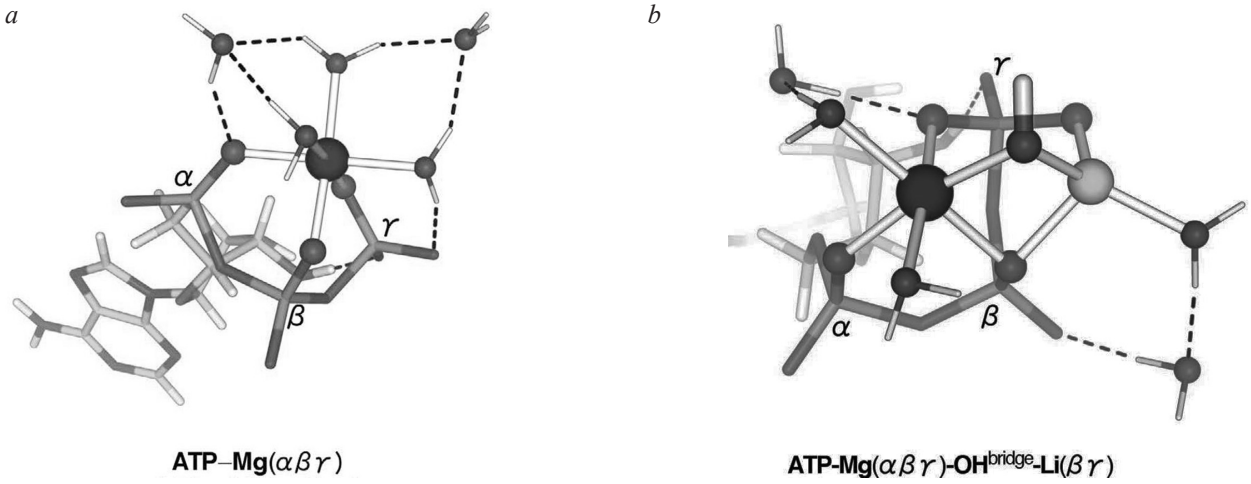

Fig. 3. M062X/6-311++G(d,p) optimized structures of the most stable (a) Mg^{2+}-ATP complex, where the metal binds in a tridentate fashion to the α, β and γ phosphates, and (b) Mg^{2+}-ATP-Li^{+} complex where Li^{+} binds to the Mg^{2+}-ATP tridentate complex in a βγ-bidentate mode via OH^{-} metal bridge [9].

the properties of the P–O bonds: The P–O bond lengths in the Mg^{2+}-ATP (Fig. 3a) and Mg^{2+}-ATP-Li^+ (Fig. 3b) complexes are identical (1.693 Å), while the bond polarities, estimated by the difference between the P and O Hirschfeld charges, are 0.81e and 0.83e, respectively.

These findings have important consequences for Mg^{2+}-ATP and Mg^{2+}-ATP-Li^+ recognition by cellular receptors. Since these two types of metal complexes have the same charge, similar overall ATP conformation and P–O bond properties, the Mg^{2+}-ATP-Li^+ complex might fit in the host receptor and trigger cellular response. Indeed, experiments show that Mg^{2+}-ATP-Li^+, like the native Mg^{2+}-ATP construct, is recognized by purinergic receptors and can activate subsequent signaling pathways [11]. Hence, Li^+ binding to Mg^{2+}-loaded ATP may permit recognition of the Mg^{2+}-ATP-Li^+ complex by certain host enzymes/receptors and activate specific signaling pathways.

Ga^{3+} vs Fe^{3+} in transferrin and ribonucleotide reductase

How selective are the metal binding sites of transferrin and ribonucleotide reductase, a key Fe^{3+} transport protein and an essential non-heme iron enzyme, respectively, for the two competing species, Ga^{3+} and Fe^{3+}? In answering this question, we have modeled the respective metal-loaded binding sites and evaluated the free energy of metal substitution [5].

The calculations demonstrate that Ga^{3+} cannot displace Fe^{3+} from a buried metal binding site evidenced by a positive ΔG^4 of metal exchange (= 0.9 kcal/mol) in Figure 4. This is in line with experimental estimates showing that the metal center, which is buried, exhibits greater affinity for Fe^{3+} than Ga^{3+} (ΔG^{exp} for $Fe^{3+}\rightarrow Ga^{3+}$ substitution = 2.4 kcal/mol [37]. However, transferrin remains the main carrier of gallium in the bloodstream as only one-third of its binding sites are loaded with Fe^{3+} [14, 24] thus the unoccupied binding centers can accomodate the incoming Ga^{3+} and, subsequently, deliver the alien metal to its target.

Ribonucleotide reductase contains two ferric-active centers which both, as the calculations imply, are prone to $Fe^{3+}\rightarrow Ga^{3+}$ substitution in solvent accessible binding pockets (negative ΔG^{32} in Figure 5). The $Fe2^{3+}$ binding site, characterized with lower free energies of metal exchange than its $Fe1^{3+}$ counterpart, seems to be the more likely target for Ga^{3+} attack. Therefore, the active sites loaded with the redox-inactive Ga^{3+} apper, in line with the postulated hypothesis (see above), defunct thus lowering the elevated levels of the enzyme in malignant cells.

CONCLUSIONS

This review summarizes the most accepted hypotheses about the mechanism of therapeutic action of the two abiogenic cations Li^+ and Ga^{3+}. Using the tools of the computational chemistry it sheds light on the intimate mechanism of the competition between Li^+ and Mg^{2+}, and Ga^{3+} and Fe^{3+} in protein binding sites. This, however, does not preclude efforts for deeper understanding the biochemistry and curative effect of abiogenic metal cations: The lithium's use as a preventive treatment for Alzheimer's disease or other neurodegenerative disorders calls for further investigations. Gallium, on the other hand, is also known for its antimicrobial and anti-inflammatory

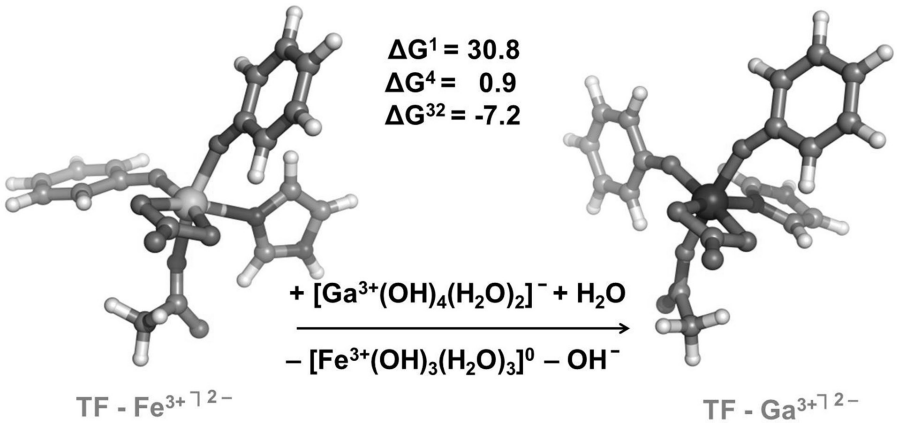

Fig. 4. ΔG^x (in kcal/mol) for $Fe^{3+}\rightarrow Ga^{3+}$ substitution in a model transferrin binding site. Calculations are performed at B3LYP/6-31+G(3d,p) level of theory [5].

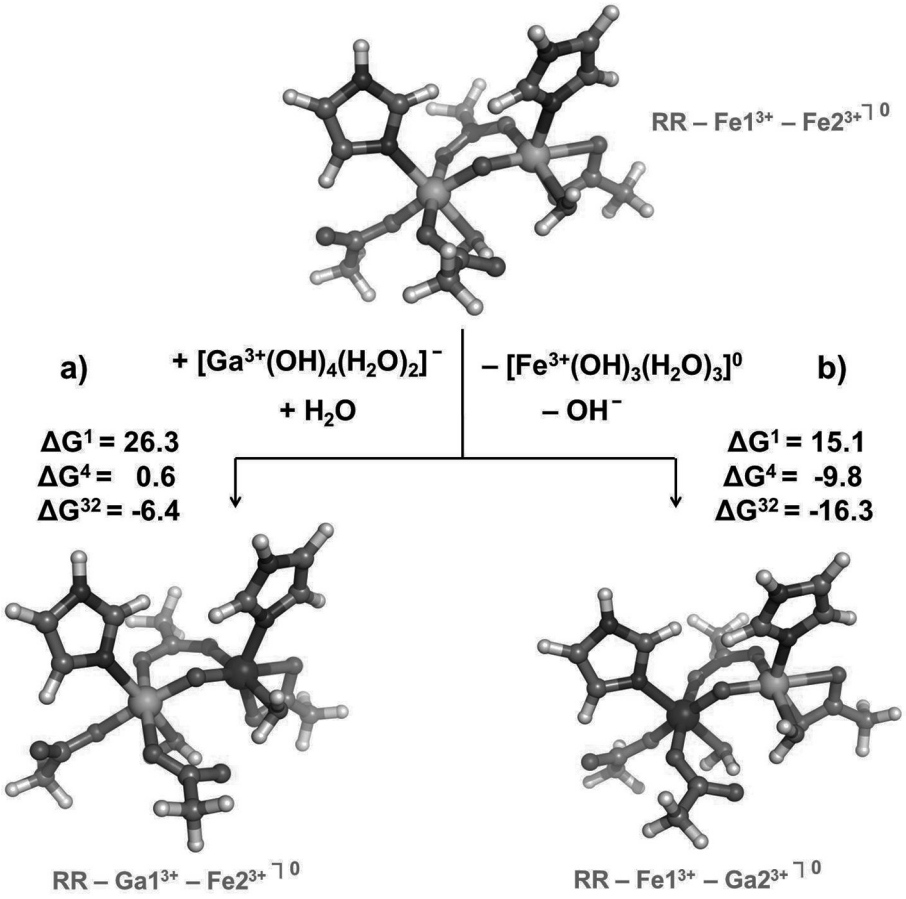

Fig. 5. ΔG^{x} (in kcal/mol) for $Fe^{3+} \rightarrow Ga^{3+}$ substitution in a model ribonucleotide reductase active center. Calculations are performed at B3LYP/6-31+G(3d,p) level of theory [5].

actions, but the underlying mechanism/s of its curative effect is/are still enigmatic. The beneficiary effect of Sr^{2+}, another abiogenic metal, for human health and its mode of action have still to be elucidated.

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МЕХАНИЗЪМ НА ТЕРАПЕВТИЧНО ДЕЙСТВИЕ НА АБИОГЕННИТЕ ЙОНИ Li^+ И Ga^{3+}: ИЗВОДИ ОТ ТЕОРЕТИЧНИ ИЗСЛЕДВАНИЯ

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(Резюме)

Литият и галият (Li^+ и Ga^{3+}) не проявяват биологични функции в живите организми и се определят като абиогенни йони. Въпреки това те се използват в медицината (под формата на разтворими соли) като лекарства от първа линия за лечението на биполярно разстройство (Li^+) и на хиперкалциемия при раково болни пациенти (Ga^{3+}), както и като лекарство с антипролиферативно действие в клинични изпитания (Ga^{3+}). Макар че терапевтичните им ефекти са добре известни, съществуват много въпроси без отговор, засягащи механизма им на действие. Основните хипотези предполагат конкуренция между Li^+ и нативния Mg^{2+}, както и между Ga^{3+} и биогенния Fe^{3+} за свързване с някои металоензими, участващи съответно в клетъчната сигнализация или делене. Проведените теоретични изследвания обясняват някои от най-широко разпространените хипотези за терапевтичното действие на двата абиогенни йона. Факторите, управляващи конкуренцията между биогенните и абиогенните катиони в активните центрове на протеините, също биват разкрити. Теоретичните резултати са в съответствие с експериментални данни от литературата.