

# Stable Magnetic Isotopes as New Trend in Nuclear Nano Biotechnology

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## ABSTRACT

With dimensions of the order of tens angstroms, biomolecular devices are assigned, in modern terminology, to objects of “nanophysics”. At the same time, all of them are composed from chemical elements many of which have magnetic and non-magnetic stable isotopes. Here I present the mini-review of our recent works in which MIE of magnesium have been revealed in living nature. Mg has three stable isotopes,  $^{24}\text{Mg}$ ,  $^{25}\text{Mg}$  and  $^{26}\text{Mg}$  with natural abundance of  $\approx 79$ , 10 and 11%, from which only  $^{25}\text{Mg}$  is magnetic isotope (nuclear spin  $I = 5/2$ ) whereas  $^{24}\text{Mg}$  and  $^{26}\text{Mg}$  are non-magnetic isotopes (nuclear spin  $I = 0$ ). In experiments with yeast cells, *S. cerevisiae*, it was revealed that enrichment of the cells with magnetic isotope,  $^{25}\text{Mg}$ , gives the two-fold increase in the rate constant of post-radiation recovery when compared to the cells enriched with the non-magnetic magnesium isotope. In experiments with another commonly accepted cell model, *E. coli*, it was revealed that bacteria essentially faster adapt to the growth media enriched with  $^{25}\text{Mg}$  by comparison to the media enriched with  $^{24}\text{Mg}$  or  $^{26}\text{Mg}$ . Furthermore, in cooperation with Palladin Institute of Biochemistry, Kyiv, Ukraine, it was revealed that  $^{25}\text{Mg}$  essentially, 2 - 2.5 times by comparison to the spin-less  $^{24}\text{Mg}$  or  $^{26}\text{Mg}$ , accelerates ATP hydrolysis driven by myosin, one of the most important protein nanoreactors of cell bioenergetics. The experimental results provide the grounds of believing that pharmaceutical agents, enriched with  $^{25}\text{Mg}$  or possibly with magnetic isotopes of some other elements, will find use in nuclear nano-biotechnology and nano-medicine for creating novel anti-stress drugs including anti-radiation protectors. Besides, they open novel ways for control over efficiency and reliability of nanoreactors in optical communications, quantum information processing, computational schemes and the like.

**Keywords:** magnetic isotopes, nuclear spin catalysis, nanoengineering, nanomedicine, reliability, robustness.

## INTRODUCTION

It is well known that biological systems are constructs, i.e., structures designed with the aim to perform predetermined functions. For example, a function of any enzyme as a biomolecular construct is

to catalyze the preset biochemical reaction. As devices with dimensions of the order of tens angstroms, enzymes are assigned, in modern terminology, to objects of “nanoengineering” – a catchall term for engineering devices sized between 1 and 100 billionths of a meter. As it is, it brings such devices down to intrinsic instability of their functional parameters due to thermal, mechanic and other fluctuations. This inevitably decreases reliability (robustness) of such a device, i.e. – its ability to perform the preset function for the given time under the given conditions [1-5].

At the same time, all biopomolecular nanoreactors, like other cell structures, are composed from atoms of chemical elements. Many of the chemical elements have magnetic and non-magnetic stable isotopes. The question arises as to whether magnetic fields of the atomic nuclei have any effects on efficiency and reliability of biomolecular nanoreactors. Here I present the mini-review of the recent works of our group in which we revealed the magnetic isotope effects (“nuclear spin catalysis”) in living cells. Moreover, the beneficial effect of the  $^{25}\text{Mg}$ ’ nuclear spin was revealed in experiments with muscle myosin, one of the most important protein nanoreactors of cell bioenergetics. The discovery of the nuclear spin catalysis in living matter enables the potential applications of the stable magnetic isotopes in biomedicine, including synthesis of novel anti-stress and radioprotective drugs. Besides, it reveals novel, based on the stable magnetic isotopes and spintronics, ways of control over efficiency and reliability of biomolecular devices.

## NUCLEAR SPIN EFFECTS IN BIOMOLECULAR NANOREACTORS

In engineering, there is the method of accelerated life testing when reliability of a device is tested under elevated loads. Similarly, an exposure of a biological object to ionizing radiation followed by analysis of the post-radiation recovery of cells and tissues can serve as the analogue to the accelerated reliability testing. Under such conditions, the failure rate drastically increases and functional loads on the systems of defense and repair correspondingly increase too [5]. Therefore, for the purpose of investigating the mechanisms and possible role of the magnetic isotopy in living nature, the recovery of cells from radiation injuries, “radiation stress”, is of special interest.

Among the most abundant cell elements, magnesium attracts the particular attention. This element has three stable isotopes,  $^{24}\text{Mg}$ ,  $^{25}\text{Mg}$  and  $^{26}\text{Mg}$  with natural abundance 78.7, 10.13 and 11.17%.  $^{25}\text{Mg}$  is magnetic (nuclear spin  $I = 5/2$ ) whereas  $^{24}\text{Mg}$  and  $^{26}\text{Mg}$  are non-magnetic (nuclear spin  $I = 0$ ) [6].

The striking effect of  $^{25}\text{Mg}$  was revealed in the experiments with commonly accepted cell model, *S. cerevisiae*. After UV irradiation, the recovery of the yeast cells enriched with magnetic  $^{25}\text{Mg}$  proceeds more effectively compared to the cells enriched with non-magnetic  $^{24}\text{Mg}$ . The rate constant of the post-radiation recovery was twice higher for the cells enriched with  $^{25}\text{Mg}$  [7, 8]. Furthermore, with another cell model, *E. coli*, it was revealed that, upon transferring into novel growth media, bacteria passed the adaptation period essentially faster if the growth medium was enriched with magnetic  $^{25}\text{Mg}$  by comparison to the media enriched with non-magnetic  $^{24}\text{Mg}$  or  $^{26}\text{Mg}$ . Besides, the ability of cells, which were previously grown on  $^{25}\text{Mg}$ , to form macro-colonies on solid nutrient surfaces has turned out to be essentially higher in comparison with the cells which were previously grown on the non-magnetic isotopes. For the non-magnetic isotopes,  $^{24}\text{Mg}$  and  $^{26}\text{Mg}$ , no differences were detected [9].

Thus, the catalytic effects of the nuclear spin of  $^{25}\text{Mg}$  in living cells were discovered. The magnetic isotope, by comparison with the non-magnetic ones, essentially accelerates adaptation of living cells to the stress conditions [7-10].

In chemistry, the so-called magnetic isotope effect (MIE) has long been known for a number of magnetic isotopes including  $^{13}\text{C}$ ,  $^{17}\text{O}$ ,  $^{29}\text{Si}$ ,  $^{33}\text{S}$ ,  $^{73}\text{Ge}$ ,  $^{117,119}\text{Sn}$ ,  $^{199,201}\text{Hg}$ ,  $^{235}\text{U}$ . MIE manifests itself in the fact that the chemical reactions exhibit different reaction rates and different yields of products according to whether the reagents contain magnetic or non-magnetic isotopes. That is a direct consequence of the law of conservation of electron angular moment (spin). Namely, the total spin of reaction products must be identical to the total spin of reactants (see [11, 12] and references therein). To lift the ban, electron spins of reactants must be changed. In the presence of multi-electron paramagnetic ions, like Fe, Co, Ni, Mn, Cu or Mo, singlet-triplet spin conversion is provided by spin-lattice relaxation mechanisms. However, in organic free radicals, spin-orbit coupling is negligibly small so that external magnetic fields are the only means to change the spin state, be it applied magnetic fields or the magnetic fields of nuclear spins. A similar spin ban arises at singlet-triplet transitions, both in small molecules and macromolecules, and, similarly, the external magnetic fields are the means to change the spin state [11, 12].

The ions of magnesium ( $\text{Mg}^{2+}$ ) serve the obligate cofactor functions for many enzymes [13]. Among them, myosin-like proteins are molecular motors

responsible for myriad biological processes such as muscle contraction, embryogenesis, and so on, for which they hydrolyze adenosine 5'-triphosphate (ATP) into adenosine 5'-diphosphate (ADP) and inorganic phosphate ( $\text{P}_i$ ). Actually, not a pure ATP molecule but the complex  $[\text{ATP}^{4-} \text{Mg}^{2+}]$  is hydrolyzed into  $[\text{ADP}^{3-} \text{Mg}^{2+}]$  and  $\text{P}_i$  in the active center of any ATP-hydrolase. At this, the released energy, about 0.54 eV at physiological conditions, is used to execute muscle contraction, etc [13-15].

We studied effects of the magnesium isotopes on the  $\text{Mg}^{2+}$ -dependent ATP hydrolase activity of the catalytic fragment (subfragment-1) of myosin isolated from myometrium muscle [16]. Three independent experiments have been done with three enzyme preparations isolated from three different animals at different times. Despite variations among mean values of the ATPase activity, stemming from the generally known variability of enzyme preparations isolated from different animals, the striking observation is that the same isotope effects have been observed in all experiments. Namely, the enzyme activity has turned out to be 2 – 2.5 times higher in the presence of magnetic  $^{25}\text{Mg}$  than the activity of the same enzyme in the presence of the non-magnetic isotopes or with natural Mg (natural isotope abundance). Figure 1 demonstrates summary of these measurements.

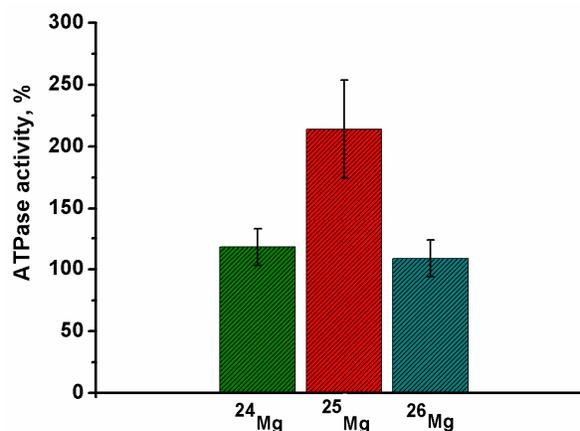


Fig. 1. ATPase activity of myosin subfragment-1 in the reaction solutions with different isotopes of magnesium, i.e., 5 mM of  $^{24}\text{MgCl}_2$ ,  $^{25}\text{MgCl}_2$  or  $^{26}\text{MgCl}_2$ , in percentage to the enzyme activity in the reaction solution with 5 mM of the “natural”  $\text{MgCl}_2$  (natural isotope abundance).

Thus, with magnetic isotope,  $^{25}\text{Mg}$ , biomolecular nanoreactors operate more effectively in comparison with non-magnetic isotopes,  $^{24}\text{Mg}$  and  $^{26}\text{Mg}$ .

On its own, factual evidence of the magnetic isotope effect unambiguously indicates that there is a spin-selective rate-limiting step in the enzymatic ATP

hydrolysis driven by myosin, and this “bottle-neck” is accelerated by the nuclear spin of  $^{25}\text{Mg}$ .

The following explanation of the catalytic effect of  $^{25}\text{Mg}$  was proposed in [17]. It was experimentally proved long ago that ATP hydrolysis triggers electron-conformational interactions in the ATP-hydrolase’s active center, thereby producing conformational deformations in the enzyme macromolecule [18]. In essence, there is a conformational excitation of the macromolecule owing to the energy released from ATP hydrolysis (for example, see [19] and references therein). Meanwhile, the energy released from ATP hydrolysis, that is about 0.54 eV, is not large enough to trigger the electron-conformational excitation of myosin into a singlet state. It is sufficient to obtain a low-level triplet state but the transition from the ground singlet state ( $S = 0$ ) into the triplet state ( $S = 1$ ) is forbidden by the spin conservation law. The magnetic isotope of  $^{25}\text{Mg}$  makes a difference. The  $^{25}\text{Mg}$  isotope’s nuclear spin eliminates the spin ban problem providing the spin conversion from the singlet state into the triplet state.

Besides, an ion-radical pair as a spin-selective “bottle-neck” in the reaction should be considered. It is well known that the exothermic reaction of ATP hydrolysis with formation of ADP and inorganic phosphate follows the basic-acid mechanism [13-15]. Hence, in the spontaneous non-enzymatic ATP hydrolysis, appearance of any free-radical or ion-radical pair as an intermediate of the reaction seems to be unlikely. Indeed, no magnetic-isotope effect has been detected in our studies of the non-enzymatic hydrolysis of ATP- $\text{Mg}^{2+}$  complexes [16].

A different situation arises in the case of ATP hydrolysis driven by myosin. Accordingly to the quantum-classical molecular mechanics calculations [15], first catalytic step in the ATPase activation of myosin during the force generating cycle is stabilization of the  $\gamma$ -phosphate of ATP in a dissociated metaphosphate. The myosin-bound ADP and  $\text{P}_i$  products of hydrolysis remain in close contact and only release later by myosin, upon rebinding to the actin filament, that is consistent with the well-known reversibility of ATP hydrolysis in myosin. The ATP hydrolysis reaction is reversible as long as the protein remains in the postrecovery–prepower stroke conformation [15]. However, under the conditions of the electron-conformational excitation of the macromolecule, in the enzyme’s active center there may be efficient transfer of the electron spin density onto  $\text{Mg}^{2+}$  from  $\text{ADP}^{3-}$ , for example, or  $\text{NH}_2$ -group of Glu459 or  $\text{OH}^-$  of water, with formation of the relevant ion-radical pair. One can further suggest that, due to the hyperfine coupling of the  $^{25}\text{Mg}$ ’s nuclear spin with the ion-radical pair’s unpaired electron, the myosin-bound intermediate ion-radical pair is converted into triplet state ( $S = 1$ ). Meanwhile the stable spin state of

the ATP-Mg complex is singlet ( $S = 0$ ). Thus, the  $^{25}\text{Mg}$  decreases probability of the undesirable reverse reaction of ATP synthesis, thereby promoting the direct reaction of ATP hydrolysis.

One way or the other, the nuclear spin of  $^{25}\text{Mg}$ , via acceleration of the chemo-mechanical cycle of the enzyme, helps in setting the myosin macromolecule for acceptance and hydrolysis of next ATP molecule.

In “molecular motors” which run on non-magnetic isotopes of magnesium, the spin-catalysis function can be served by the nuclear spins of phosphorus and protons. However,  $^{25}\text{Mg}$  has the nuclear spin 5/2, that is five times greater than the nuclear spins of  $^{31}\text{P}$  or  $^1\text{H}$ . Furthermore, the comparatively high catalytic activity of the  $^{25}\text{Mg}$ ’s nuclear spin may stem from the specific beneficial localization of  $\text{Mg}^{2+}$  ion in the enzyme active center due to which the magnesium’s nuclear spin creates the comparatively higher values of the magnetic field and hyperfine coupling. That is why  $^{25}\text{Mg}$  proved to be “in the right place at the right time” to perform the nuclear spin catalysis in the biomolecular nanoreactors. The detailed mechanisms, including quantum mechanics, of the nuclear spin catalysis in living cells require further investigations.

## CONCLUSIONS AND PROSPECTS

It can be suggested that beneficial effects of the magnetic isotope of magnesium detected in experiments with isotopically enriched bacterial cells (acceleration of adaptation to a new growth medium) and yeast cells (acceleration of post-radiation recovery) would provide the possibility of new anti-stress agents based on the magnesium magnetic isotope, in particular, new means for protection against ionizing radiation, i.e., low-toxicity radiation protectors, suitable for long-term use as nutrition additives [17].

In living Nature, apart from magnesium, there are other elements which have both kinds of stable isotopes, non-magnetic and magnetic ones, including carbon, oxygen, calcium, zinc, etc. In the magnetic field of Earth, the strength of which is about 0.05 mT, NMR frequencies of the nuclei fall within the range between approximately 50 and 2000 Hz. Biological effects of weak low-frequency magnetic fields are well known for a long time but poorly understood [20]. Inasmuch as the nuclear spin moments of the magnetic isotopes are prone to external magnetic fields, it may bear a direct relationship to the biological effects of the electromagnetic environment.

Furthermore, the geocosmic oscillations in processes of different nature, caused by movement of the Earth in heterogeneous and anisotropic space-time, have long been known. For example, the macroscopic fluctuations as the anomalous scattering of the results of measuring the actomyosin enzyme activity were discovered about sixty years ago [21]. Based on the

nuclear spin-catalysis background, one can suggest that the above mentioned macroscopic fluctuations in the actomyosin and some other objects of living Nature may stem from the interactions of the nuclear spins of the magnetic isotopes with the oscillating geocosmic electromagnetic fields.

Based on the same nuclear spin-catalysis background, one can further speculate that stable magnetic isotopes hold considerable promise for control over efficiency and reliability of molecular and biomolecular devices in optical communications, quantum information processing, computational schemes and the like.

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