Change of $^{2}H/^{1}H$ Ratio and Adaptive Potential in Living Systems under Formation of Isotope Gradient

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Abstract: This article presents data on ability of drinking water with depleted concentrations of deuterium (deuterim depleted water – DDW, $\delta^{2}H$ = -762 ‰) to influence on the adaptive capacities and functional activity of rats organism during long period of DDW consumption. The obtained data confirms the favorable effect of reduced $\delta^{2}H$ on hepatocytes of medium and shows significant (by 10%) increase of body weight among rats which consumed DDW for 3 weeks after birth. It is also shown that when rats consumed DDW, the non-uniform distribution of deuterium in the blood plasma and liver, kidney and heart tissues is observed. At the same time under natural conditions $\delta^{2}H$ was significantly lower in blood plasma than in tissues of internal organs ($\delta^{2}H$ plasma > $\delta^{2}H$ of tissues of internal organs), whereas DDW consumption resulted in more significant decrease of $\delta^{2}H$ level in blood plasma than in the internal organs, which phenomena was accompanied by change of direction of $^{2}H/^{1}H$ isotope gradient: $\delta^{2}H$ of plasma < $\delta^{2}H$ of tissue of internal organs. Stable change in direction of $^{2}H/^{1}H$ isotope gradient over 3 weeks is expressed by lower rate of weight gain in the first generation of rats. All these facts can be caused by influence of $^{2}H/^{1}H$ isotope gradient on long-term adaptation mechanisms, but not on short-term adaptation reactions. Decrease of $\delta^{2}H$ in blood plasma and tissues of internal organs increases to a greater extent the resistance of an organism to influence of unfavorable environmental factors among future generations of rats consuming DDW for a long time.

Keywords: Deuterium, living systems, isotope, deuterium depleted water.

INTRODUCTION

In nature the fractionation of isotopes is more expressed in those elements which more actively participate in various biological processes [1-3]. The particular importance is conferred upon distribution of heavy non-radioactive isotopes of hydrogen ($^{2}H/^{1}H$) and oxygen ($^{18}O/^{16}O$) [4]. At the same time the attention of scientists is often paid to study of isotopic composition in blood, urine and skin appendages [5-8], but distribution of isotopes in tissues of internal organs and its influence on growth and development of future generations is not sufficiently studied.

There are significant researches of biological effects related to increase of light isotopes content in a body, including through the drinking ration deuterium depleted water (DDW), which can be used to correct metabolic disorders in various diseases, [9-12], however, mechanisms of the described effects have not yet been studied in details [13, 14].

Thus in range of studies the various effects have been described, arising both due to consumption of DDW by laboratory animals and due to cultivation of different cell cultures in deuterium depleted content media [15]. At the cellular level the studies are conducted to find out the effect of DDW on oncoculture; Cong F.-S. *et al*. showed that DDW induces apoptosis in human lung carcinoma cell line A549 *in vitro*, and also reduces lung tumor size in mice *in vivo* by 30% [16]; and Wang H. *et al*. showed the efficiency of DDW to inhibit the proliferation of nasopharyngeal carcinoma cells [17]. In addition, studies are conducted of DDW influence for dynamics of growth and activity of various microorganisms, for example it is shown that yeast cells, taken as tested objects, double increase production of CO_2 yield in a nutrient mixture prepared in light water with depleted content of deuterium [18].

The recent study showed a significant correlation (Pearson's r = 0.468; p = 0.0016) between deuterium content in drinking water and rates of depression. It was estimated that prevalence of depression is increased by 1.8% (p = 0.0016) for a 10 ppm increase in deuterium concentration of drinking water. In addition, there was observed an increased stress resistance in laboratory mice that consumed DDW

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during stress modeling [19]. Another study noted an improvement in long-term memory in rats that consumed DDW for a long time [20]. To understand the above-described effects, it is important not only to determine the concentration of deuterium in biological fluids, but also to study its distribution in tissues directly.

The purpose of the study was to define the adaptation potential in rats and $^2H/^1H$ ratios in blood and internal tissues when forming a concentration gradient of non-radioactive hydrogen isotopes along with decreasing of deuterium content in water (δ^2H = -762 ‰).

MATERIALS AND METHODS

The research was conducted on rats of the *Wistar* line, 30 animals in each study group, each composed of 6 males and 24 females. The first generation consisted of rats aged 4 months (body weight 225 ± 12 g), which were divided into 2 groups: I (n = 15, 3 males and 15 females) and II (n = 15, 3 males and 15 females) – depending on isotopic composition of water in their diet. In group I all generations of animals (groups I_{a-c}) was fed by usual diet and DDW (δ^2H = -762 ‰, hereinafter referred to as deuterium content) during all the experiment. In Group II the animals of all generations (groups II_{a-c}) were fed by the usual food ration and mineralized water δ^2H = -24 ‰ during all the experiment. Subsequently the animals born in groups I_a and II_a made the second generation of the rats, the I_b groups (n = 15) and II_b (n = 15), respectively, and their descendants then formed the groups I_c and II_c, and so on. In groups I_a and II_a the isotopic composition of blood plasma was studied every week during 4 weeks after start of the experiment, and measurements of tissues of internal organs (liver, kidney, heart) were taken at the end of the experiment in the fourth week. Blood was taken from the tail vein of all the experimental animals in group I_a. Blood was taken from the tail blood in all groups of "b" and "c" generations to study its isotope composition, and lyophilized tissues (liver, heart, kidney) were studies on the 6^{th} month of development. In addition we weighed these animals during 3 weeks in groups I_a, I_c and II_a, II_c to evaluate the effect of isotopic exchange reactions (^2H / ^1H) on weight gain among adult rats (group I_a) after administration of DDW to their diet and among newborn rats (group I_c) in the first 3 weeks after birth. Moreover the parents of the newborn rats (group II_a) also received deuterium depleted water (δ^2H = -762 ‰) throughout the ontogeny. In addition to body weight (at 1, 2, 3 and 4 weeks) the mass of internal organs was also measured in the fourth week, including liver, kidney, and heart, in order to determine the effect of isotopic exchange reactions on a body condition – all measurements were made with accuracy of ± 0.001 g (Acculab Vicon, USA). Further on the basis of obtained data we calculated the integral indicator of chronic intoxication (IICI), which was calculated by the formula: $m_1 / m_2 \cdot 100\%$, where m_1 is the mass of the internal organ (liver, kidney, heart), m_2 is the body mass of the animal. The obtained results of IICI were expressed in conventional units (conv. un.).

All animals were kept in a vivarium in similar conditions i.e. temperature, humidity, lighting; and also received the same food ration. Laboratory rats were kept in a vivarium at an air temperature of +20 to +22 ° C, humidity – no more than 50%, lighting mode – day-night. The animals were placed in the same plastic cages and kept on a standard food ration of a vivarium.

Deuterium depleted water was obtained in the aggregate developed in the Kuban State University [21]. The initial concentration of deuterium in the produced water was δ^2H = -762 ‰. The obtained water was mineralized by the addition of mineral salts into water in order to obtain a physiologically appropriate mineral composition (mineralization 314-382 mg./l.: hydrogen carbonates of 144-180 mg., sulfates less than 1 mg., chlorides 60-76 mg., calcium: 6 mg., magnesium: 3 mg., sodium 50-58 mg., potassium 50-58 mg.), which value was identical to this value in water with deuterium content of δ^2H = -762 ‰ and δ^2H = -24 ‰.

In addition during the whole experiment, the physical activity of animals, their appetite and features of their stool were observed. Also, a daily clinical examination, animals weighing, and rate of DDW consumption (per each laboratory rat) were performed daily. All studies were performed approximately at the same time before feeding of the animals. The survival of the experimental animals in control and experimental groups I_a and I_b was complete (100%) throughout the whole experiment, and in the I_{b-c} and II_{b-c} groups it was 90-93% and 80-93%, respectively.

Deuterium concentration in the obtained water was determined by impulse NMR spectrometer JEOL JNM-ECA 400MHz (Jeol, Japan) by the method: FR.1.31.1999.00073 “Method of measuring of deuterium content in water, aqueous-organic and organic solutions by nuclear magnetic resonance spectroscopy” [22].

The mass spectrometer DELTA^{plus} (Finnigan, Germany) was used to determine the isotopic composition of lyophilized organs of laboratory animals [23]. The fluctuation of deuterium in blood and lyophilized tissues in the control group in all generations (II_{a-c}) did not exceed 1%, which allowed deriving the average control value of the deuterium content for each studied organ and blood plasma.

Statistical processing of the obtained data was carried out using variation statistic methods with free software – the statistical analysis system R (R Development Core Team, 2008, the difference at $p < 0.05$ was considered as reliable).

RESULTS

The significant change in the isotopic composition of blood plasma and tissues of internal organs was found, depending on drinking ration. At the same time, the fastest decrease in deuterium content (observed already in the first week of the experiment) was noted in blood plasma of the rats in group I_a (Figure **1**). In the future the rate of decrease in deuterium concentration in blood plasma slowed down (from 42% in the second week to 17% in the third week) and, starting from the fourth week, the isotope equilibrium was reached within the range from -359 to -342 ‰.

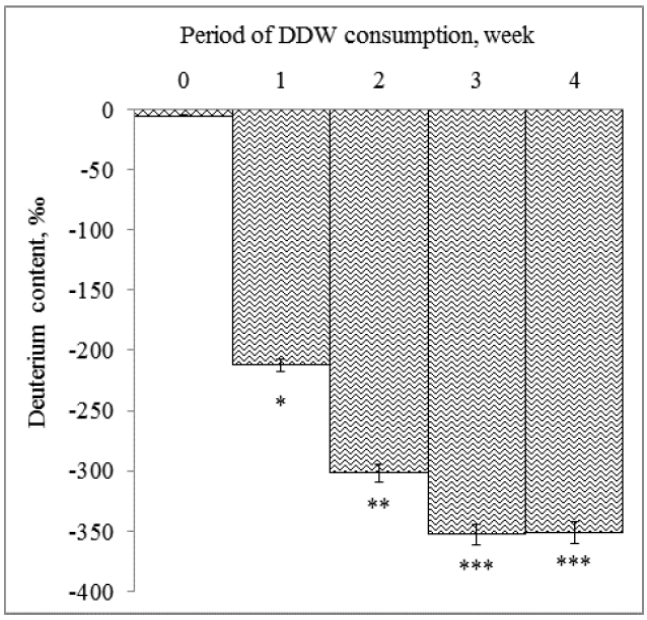

Figure 1: Reduction of deuterium content in blood plasma of laboratory animals during consumption of water with deuterium concentration δD= –762 ‰.

Note: * - $p < 0.05$ in comparison with deuterium content at the beginning of the experiment; ** - $p < 0.05$ in comparison with deuterium content at the end of the first week of the experiment; *** - $p < 0.05$ in comparison with deuterium content at the end of the second week of the experiment.

When DDW was used among rats in group I_a, decrease in δ^2H content occurred within 4 weeks and a new equilibrium condition of ^2H / ^1H was reached, which was 15.3 times lower than that in group II_a (Figure **2A**), whereas in liver, kidney and the decrease of δ^2H in comparison with blood plasma was 1.57 times (Figure **2D**), 1.49 times (Figure **2C**), 1.52 times lower than group II_a (Figure **2B**) taken as 100.0% (Figure **2**).

In metabolically active organs, for example, in the liver, DDW is able to reduce the toxic effect of endogenous substrates onto cells [9], which is confirmed by this completed experiment by lower value (by 13%) of IICI in liver observed in group I_b (Table **1**).

DISCUSSION

The constant presence of DDW in a diet allowed reaching of stable ^2H / ^1H isotope equilibrium already in generation I_b. In group I_a the changes in δ^2H reached at the fastest rate the equilibrium in the liver and heart, characterized by a high level of metabolism. Nevertheless the values of ^2H in these organs still remained above these values in blood plasma, which may be caused by active inflow of nutrients in the hepatocytes and cardiomyocytes with a higher ^2H content than in consumed water, since it is known that by drinking diet is possible to replace no more than 30% HDO in the cells [24]. The ^2H content in blood plasma exceeded these values in tissues of internal organs within the range from 101 to 170 ‰ among the rats of group II_a (Figure **2A-D**), whereas after the rats drank DDW, the level of δ^2H in tissues of their internal organs exceeded this level in blood plasma. All this was generally accompanied by a change in the direction of $^2H/^1H$ isotope gradient, which under natural conditions was δ^2Hplasma > δ^2Htissue, whereas among the rats from DDW consuming group, the direction of this gradient changed to the opposite: δ^2Hplasma <δ^2Htissue.

In addition the animals in group I_a, showed change in body mass dynamics: during the first week the weight gain was negative, the greatest decrease was observed at the beginning of the second week (-5% of the initial values), and from the third week positive growth rates body weight (4%) was observed, which reached 16% in 4 weeks ($p < 0.05$ in comparison with group II_a). At the same time in group II_a the positive body weight gain was observed throughout the whole experiment at 4%, 10% and 23% in the second, third and fourth weeks, respectively.

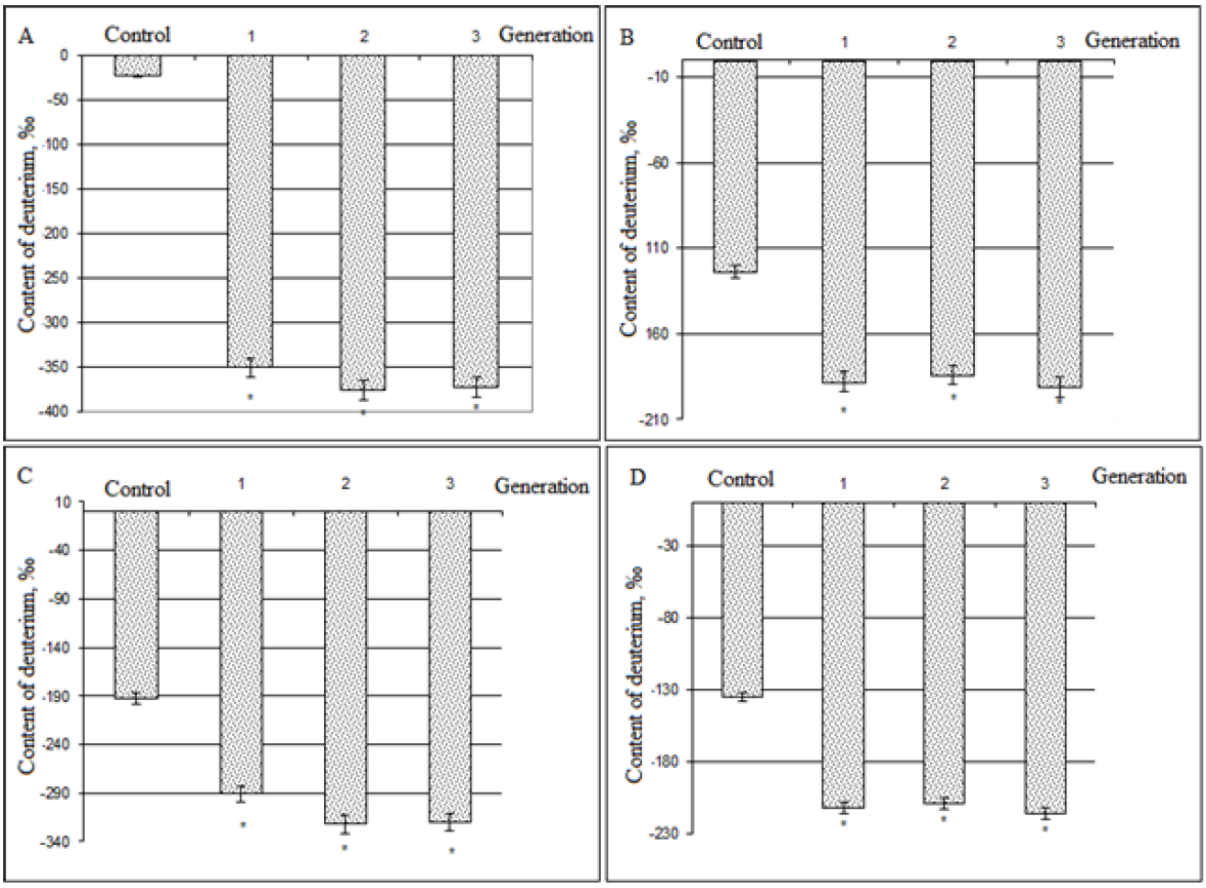

Figure 2: δ^2H in blood plasma and heart tissues, kidney, liver in rats consuming drinking water with δ^2H = -762 ‰ and δ^2H = -24 ‰.

Note: * - p <0.05 in comparison with the control group; 1 – the first generation of rats (I_a), 2 - the second generation of rats (I_b), 3 – the third generation of rats (I_c), 1-3 – rats consuming DDW with δ^2H = -762 ‰, control – rats consuming DDW with δ^2H = -24 ‰. A – blood plasma, B – heart, C – kidney, D – liver.

Table 1: The Integral Index of Chronic Intoxication (IICI) in Rats with DDW Drinking Diet δD = -762 ‰ and δD = -24 ‰

# of the group	Integral index of chronic intoxication, cond. un.		
	Kidney	Liver	Heart
Group I_a	0.33 ± 0.04	2.54 ± 0.07	0.35 ± 0.02
Group II_a	0.34 ± 0.06	2.93 ± 0.12 *	0.36 ± 0.05

Note: * – p < 0.05 in comparison with group I_a.

The above described changes in body weight among rats can be explained by “isotopic shock” [25], which led to activation of nonspecific defense system of a body, which is related to modulating effect of δ^2H (reduced in comparison with natural) on cells of various organs [26], as well as change in direction of $^2H/^1H$ isotope gradient and striving of living systems to restore the isotope composition in accordance with the natural concentrations of non-radioactive isotopes. It is known that change in rate of exchange in hydrogen atoms bound to nitrogen: = N-H → = N-D, including biomolecules containing chemical groups with hydrogen bonds (for example = N-H ... O = C =) can change by several times depending on deuterium content [27], which probably plays an important role, for example, in process of DNA replication and formation of informational RNA in metabolically active cells. In this regard the stable decrease of δ^2H in blood in 3 weeks leads to increase in adaptive capacity of the whole organism, which is confirmed by the dynamics of body weight among rats of the third generation, whose weight in the group I_c in the first week after birth was less than in group II_c at 15 %, at the end of the second week there were no statistically significant differences in body mass between groups I_c and II_c, and at the end of the 3rd week the body mass values in group I_c

exceeded by 10% these values in group II_c, which also showed a faster increase in adaptive capacity in rats in group I_c in comparison with group I_a.

Among the possible mechanisms of isotope fractionation it is necessary to take into account the presence of histogematic barriers, whose function is to ensure selective permeability for organic and inorganic molecules. The differences of isotopic composition for different internal organs can be caused also by differences of metabolic processes intensity in various tissues; for example, in case of increased energy production there is an increased formation of water inside cells from hydrogen isotopes that are part of biological substrates of oxidation, i.e. different classes of organic compounds. At the same time intracellularly formed water can significantly differ in deuterium content from extracellular water, replenished to a body, mainly, with the food of a diet.

The above-described effect of $^2H/^1H$ isotopic exchange reactions on morphological parameters among group I_a can also be explained by replacement of deuterium by protium in HO–, HS–, and H_2N– groups of functionally active macromolecules, primarily in the active and allosteric centers of enzymes, and also by decrease in concentration of HDO in hydrate shell of proteins and nucleic acids, which can lead to change in its thermodynamic and, consequently, thermokinetic parameters, thus stimulating metabolic and mitogenic processes in cells.

CONCLUSION

Decreased δ^2H value in a medium can increase the adaptive capacity and contribute to increase of cell functional activity related to enhancement of hydrogen ions flow. This statement is confirmed by the data about infusoria *S. ambigua* cell death rate, which depended on $^2H/^1H$ ratio [13]. The latter can be compensated by more efficient work under conditions of reduced δ^2H in medium of transmembrane gradient of protons required for operation of ATP-synthase and other key enzymes in energy cycle [28]. In general, it is necessary to note that a medium with reduced δ^2H content creates favorable conditions for cells adaptation within 3 weeks after birth in the third generation of laboratory rats consuming DDW (that may be explain involve by the membrane ion transport systems for example, acid-sensing or transient receptor potential cation channels [20, 29]). Thus, during the experiments on laboratory animals, uneven (non-uniform) distribution of deuterium in liver, kidney and heart tissues was found, which level of δ^2H under natural conditions was significantly lower than its level in blood plasma: δ^2H plasma> δ^2H of internal organs tissue. The use of DDW led to the most significant decrease in δ^2H in blood plasma than in internal organs (1.2 - 1.8 times less), which was accompanied by a change in the direction of ^2H / ^1H isotope gradient (δ^2H plasma <δ^2H of internal organs tissue). A stable change in direction of $^2H/^1H$ isotope gradient during 3-4 weeks is expressed by lower rate of weight gain in the first generation of rats and faster rate of weight gain in the third generation of rats, which is apparently related to effect of ^2H / ^1H isotope gradient on long-term adaptation mechanisms. In addition, introduction of DDW into drinking diet according to IICI data reduces toxic load on hepatocytes in the first generation of rats by 13%, which also increases the resistance of a whole organism to influence of unfavorable environmental factors.

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