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Hereditary component of variation in ^{90}Sr deposition in inbred mice under exogenous conditions that affect bone formation

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HIGHLIGHTS

- The heredity of ^{90}Sr metabolism in mice is established and its sustainability is investigated.
- Experimental groups were formed comprising offspring of the same litter.
- The effects of sex, age, developmental conditions, and litter size were estimated.
- Results were correlated with morphological features with known hereditary influence.
- The results indicate a stable hereditary component of ^{90}Sr deposition.

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ABSTRACT

Bone-seeking radionuclides (specifically ^{90}Sr) accumulate in the bone tissue and act as a long-term source of internal irradiation. Their behaviour in the body has been studied in detail, while the impact of inheritance has not been established. On one hand, the genetic determination of both skeletal morphology and calcium metabolism is indirect evidence that the kinetics of deposition of alkaline-earth radioisotopes in the skeleton also have a hereditary component. On the other hand, analysis of ^{90}Sr kinetics in different inbred mouse strains did not reveal any differences between the mice. This study used a classical approach to evaluating the hereditary component of variation in quantitative traits, namely, a variant of familial analysis (the method of twin families). The growth of the skeleton is known to be accompanied by distinct changes in ^{90}Sr accumulation. That is why the hereditary (familial) component of variation in ^{90}Sr kinetics in the bone tissue of CBA mice was analyzed under the influences that modify growth processes Individual parameters of ^{90}Sr accumulation differed between experimental groups by a factor of 2–4.5. At the same time, features of ^{90}Sr accumulation proved to be characteristic of entire families. The results show that the intrafamilial correlation in ^{90}Sr deposition in the skeleton is highly significant ($R = 0.542$, $P \leq 0.0001$) and comparable to that of morphological parameters ($R = 0.532$–0.546, $P \leq 0.0001$). The results confirm the existence of statistically significant intrafamilial correlations of weight and metabolic parameters, which is similarly expressed in different families, thereby providing evidence for hereditary determination of ^{90}Sr metabolism. At the same time, the stability of ^{90}Sr metabolism inheritance to changes in morphophysiology and environmental influences (including those close to pathogenic ones) is shown. This is evidence of its authenticity and significance. The results obtained can be extrapolated to humans instead of directly analyzing the role of hereditary factors in the metabolism of toxic compounds, which are difficult and unethical to perform in human subjects.

1. Introduction

Bone-seeking radionuclides, in particular ^{90}Sr, are technogenic pollutants of high-priority concern. This concern is due to their impact on the health of professionals employed in the radiation industries and of large population groups and livestock in the zones of major nuclear accidents (e.g., at Kyshtym, 1957; Chernobyl, 1986; Windscale, 1957) (Alexakhin et al., 2004; ICRP, 2007, 2009). Up to 90% of radionuclides entering the body selectively accumulate in the skeleton, fixed on the surface or within the bone tissue.

The behaviour of bone-seeking radionuclides in the bodies of vertebrates has been studied in sufficient detail (Stover, 1959; Strontium Metabolism, 1967; ICRP, 1973; Vaughan, 1981; Harmful Chemical..., 1990; Starichenko et al., 1993; Shvedov and Akleyev, 2001). As shown

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in laboratory experiments, metabolic and kinetic parameters differ significantly among animals of the same age and sex. Therefore, individual analyses based on average values of these parameters can lead to serious errors in evaluating the kinetics of radionuclides (Likhtarev et al., 1975; Thomas et al., 1984; ICRP, 2007) and the dose of internal irradiation. For example, the effect of internal irradiation may differ by an order of magnitude because of individual variation in the kinetics of the radionuclide (Lyubashevsky et al., 1989). Reviews of relevant studies and the authors' concepts of mechanisms responsible for the metabolism of radionuclides and stable bone-seeking substances have been presented in previous publications (Lyubashevsky, 1980; Starichenko et al., 1993; Starichenko, 2007; Starichenko and Lyubashevsky, 2009).

The problem of hereditary determination in the kinetics of bone-seeking radionuclides has been studied and discussed for more than half of a century. An argument for this determination comes from the data on the stability of parameters of radionuclide metabolism, which hardly change even under sublethal influences, such as the extirpation of internal organs (Stepina et al., 1973). Moreover, the metabolism of alkaline-earth isotopes is closely associated with calcium metabolism in the bone, which has been extensively studied because of its relevance to the worldwide problem of osteoporosis (Slemenda et al., 1996; Rosen et al., 2001; Ralston and Crombrugghe, 2006, etc.) and has been shown to be genetically determined.

However, these data provide only circumstantial evidence for the hereditary determination of bone-seeking radionuclide metabolism with no empirical proof. Genetic control of the metabolism of bone-seeking substances in vertebrates, including humans, is hardly probable. A major argument against the genetic inheritance of their metabolism is provided by the results of experimental studies (including ours) on ^{90}Sr kinetics in inbred mouse strains. The criterion of inheritance (inheritance test) of a trait can be its quantitative dependence on belonging to a certain genotype (inbred mouse strains) (Shvedov, 1965; Starichenko et al., 1993; Shvedov and Akleyev, 2001). Indeed, the tested strains differ in radiosensitivity by a factor of 1.5–2. However, the dependence of accumulation of ^{90}Sr in the skeleton on the genotype (strain) of animals was not detected, the inheritance test of bone-seeking radionuclides metabolism was negative (Shvedov, 1965; Starichenko et al., 1993). The only exception is a study (Senjuk et al., 2013) in which the authors revealed interstrain differences in the accumulation of ^{90}Sr ingested from contaminated natural food.

Thus, the problem is still unresolved. To elucidate the problem experimentally, it seems necessary to use a reliable method that has not yet been used for this purpose, namely, familial analysis. This is a classical approach to evaluating the hereditary component of variation in quantitative traits, with its variants including, for example, a combination of twins analysis and familial methods (twin family study). In this case, the data analysis does not require any genetic concept.

Current investigation is a continuation of the study of hereditary (epigenetic) factors of ^{90}Sr accumulation in mammalian skeleton based on mouse models (Starichenko, 2010). For this purpose, a method of family analysis for one mouse strain is used. Since all mice of the strain have the same genotype, family analysis can identify possible epigenetic effects modifying ^{90}Sr accumulation in mouse skeleton. As it was shown earlier with the use of CBA mice (Starichenko, 2010), there is a significant intrafamily correlation of ^{90}Sr body accumulation. In current study, additional external impacts were used to analyse the stability of intrafamily correlations. For this purpose, each litter ("family") studied was divided in halfand each part was subjected to different factors modified skeleton development.

The purpose of this study was to demonstrate the existence of the hereditary (familial) component of variation in the kinetics of ^{90}Sr and to estimate the magnitude of the variation under exogenous influences that affect the processes of skeleton formation.

Verification of the hereditary component of radionuclide (in particular, ^{90}Sr) metabolism is a current problem in radiology and radioecology (Shvedov and Akleyev, 2001; Fogelman et al., 2012). It is directly related to the provision of medical and biological support for labour activities involving exposure to bone-seeking toxic substances (Lavryashina et al., 2003; Vogel and Motulsky, 2010; ICRP, 2016) or pathological loads on the osteoarticular system (Oganov, 2003; Ralston and Crombrugghe, 2006).

2. Materials and methods

The study was performed on CBA mice (n = 378) under two sets of exogenous conditions that affect the processes of skeleton formation:

(1) To modify growth processes, the females after childbirth were immediately placed on an unbalanced diet consisting only of oats (in balanced diet of laboratory mice, the oat content should not exceed 30% of the total volume), and their offspring continued to receive this monodiet after weaning. As shown in our previous study (Starichenko et al., 1993), such a dietary regimen leads to retardation of growth processes, including the growth of the skeleton (the prenatal effect of monodiet is relatively small, and is almost completely compensated by the maternal organism), and the return to a well-balanced diet results in gradual normalization of weight parameters.
(2) To modify bone remodeling, the mice were treated with dihydrotachysterol, a synthetic bone resorption stimulant (RS) that modulates the metabolism of bone and cartilage tissues. The RS was administered with food four times at one-day intervals (see below).

To avoid dietary deficiency of vitamins and calcium, all mice (including those on the monodiet) also received fresh greens and were supplied in excess with pieces of lump chalk as a mineral supplement.

Females with their litters (families) immediately after delivery were divided into two groups: "control" (fed standard diet) and "monodiet" (fed only oats). The pups of each group were separated from their mothers at the age of 1 month and, in turn, were divided into two groups. Half of the control animals were subsequently treated with RS (Fig. 1), with the other half remaining untreated. Half of the animals on the monodiet continued to be fed only oats until the end of experiment (the "monodiet" group), while the other half started to receive the standard diet at the age of 4 weeks (the "monodiet cessation" group). Note that the litter of one female (family) was divided between

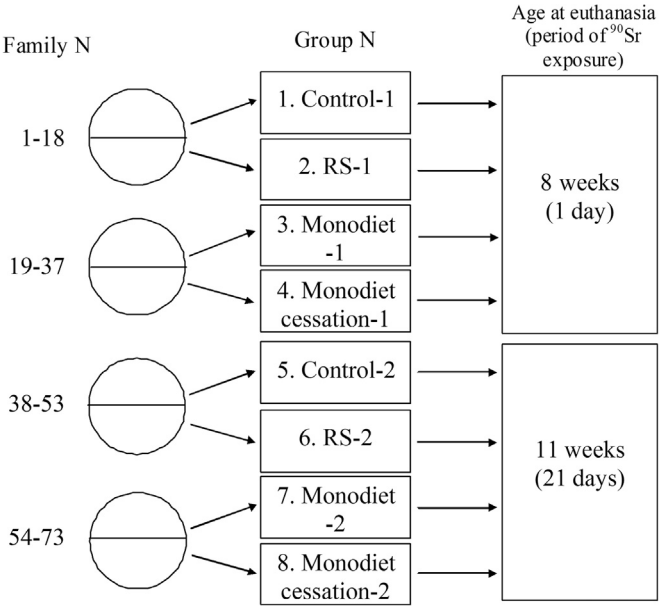

Fig. 1. Schematic of the distribution of families by experimental groups and the age of animals at euthanasia.