RESPONSE OF THE PITUITARY–ADRENOCORTICAL SYSTEM TO PROLONGED ACTION OF SMALL DOSES RELEASED FROM AN INTERNAL DEPOT OF [^{75}Se] SELENOMETHIONINE

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The principles governing the distribution of the absorbed dose and the dynamics of its formation were studied by a radiometric technique in vivo during the course of 1 year after injection of 0.033 μCi/g of [^{75}Se] selenomethionine into rats and the functional state of the pituitary–adrenal adaptive system was studied at the same time by determination of the plasma corticosterone level. The preparation was shown to have high affinity for the organs of the endocrine system. Evidence of increased functional activity of the adaptation system was given by an increase in the corticosterone concentration in the animals' blood plasma after injection of the radioactive preparation, which was significantly higher than in the control 3, 6, and 10 months after the beginning of the experiments. Exposure to acute stress (induced by histamine and formalin) 10 months after injection of [^{75}Se] selenomethionine did not produce the sharp increase in the plasma corticosterone concentration characteristic of the control rats; this points to extreme stress of the pituitary–adrenal system and its inability to respond to additional loads. It is postulated that analysis of the functional state of the adaptation system could provide the key to the assessment of the biological effect of small doses of radiation.

KEY WORDS: pituitary–adrenocortical system; adaptation; [^{75}Se] selenomethionine; stress.

In connection with the widespread use of sources of ionizing radiation in different spheres of human activity the need has arisen for an assessment of the consequences of prolonged exposure to radiation and, in particular, that due to radioactive substances entering the body. The late effects, especially their noncancerous manifestations, develop in the absence of clinical signs of illness, and the compensatory powers of the body mask their course for a certain length of time [13]. Hence the need for the study of the influence of small doses of ionizing radiation on the hypothalamic–pituitary–adrenocortical system, responsible for the course of protective, adaptive, and compensatory reactions of the body to unfavorable external environmental factors.

Most of the data obtained by investigation of the adaptive system and its components at various times after irradiation relate to external irradiation [11, 14]. In a few publications the components of the system have been studied following the intake of isotopes in large doses [1-4, 9], and in a few publications following administration of small doses of isotopes [6, 7, 10, 12]. The object of the present investigation was to study the functional state of this adaptive system and, in particular, in the late periods after the action of small doses of [^{75}Se] selenomethionine on the body. This radioactive preparation is used in clinical practice and precise guide lines for its use in isotope diagnosis need to be established [5, 8, 16, 17].

EXPERIMENTAL METHOD

Experiments were carried out on male WAG rats weighing initially 160-200 g. A single intravenous injection of [^{75}Se] selenomethionine was given in a dose of 0.033 μCi/g body weight in a volume of 0.5 ml. Physiological saline was injected into the animals of the control group. To determine the pattern of distribution of the absorbed dose in the body and the dynamics of formation of the absorbed dose during the year after injection

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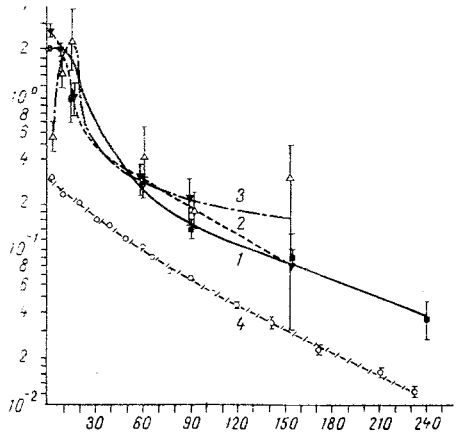

Fig. 1

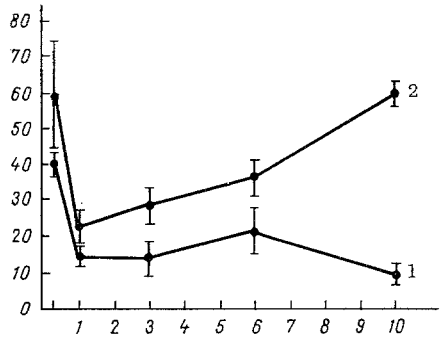

Fig. 2

Fig. 1. Changes in ^{75}Se concentration in organs and whole body of rats, shown as a percentage of injected dose, plotted against time after single injection of [^{75}Se] selenomethionine. Abscissa, time (in days); ordinate, ratio between specific activity in tissue and total initial activity in whole body × 100; 1) adrenals; 2) anterior lobe of pituitary; 3) posterior lobe of pituitary; 4) whole body.

Fig. 2. Dynamics of changes in plasma corticosterone concentration of control rats and after a single injection of [^{75}Se] selenomethionine. Abscissa, time after irradiation (in months); ordinate, plasma cortisol concentration (in μg/100 ml); 1) control; 2) injection of [^{75}Se] selenomethionine.

of the radioactive substance, a radiometric study was undertaken of the rats in vivo and also of the principal organs which accumulate this substance, including the endocrine glands.

The functional state of the adaptive system was judged from changes in the plasma corticosterone concentration and the ability of the animals to respond to acute stress. The corticosterone level was determined 1, 3, 6, and 10 months after injection of the isotope by Murphy's competitive binding method, using components of the Cortkit-^{125}I and Cortkit-^{3}H (from Sorin, France). Acute stress was induced by intraperitoneal injection of histamine (1 mg/100 g body weight) and intramuscular injection of 10% formalin 30 min before decapitation of the animals. Three series of experiments were carried out (in each experiment five animals were used at one time point).

EXPERIMENTAL RESULTS

The results of whole-body radiometry of the rats in vivo showed that [^{75}Se] selenomethionine is retained for a long time in the body and can still be detected 12 months after injection; however, 80% of the total absorbed dose (the mean for the body as a whole) accumulates during the first 3 months. The results of radiometry of the individual organs demonstrated the high affinity of the preparation for organs of the endocrine system (Fig. 1); consequently, as calculations showed, the mean tissue dose in the pituitary and adrenals was about 1.5 times greater than the mean load on the body as a whole, and in the present experiments it was 10 and 7 times respectively.

Analysis of the changes in the blood plasma corticosterone concentration in the animals of the control group showed definite fluctuation throughout the period of the experiments (Fig. 2). These changes were connected with the seasons of the year, and in the winter months the level of the hormone was particularly low. An increase in the hormone concentration was observed 1 week after injection of [^{75}Se] selenomethionine in the animals of the experimental group, but it was not regular. A tendency for the corticosterone concentration to rise was observed in the animals of the experimental group from 1 to 3 months after injection of the isotope. A significant increase in the plasma corticosterone concentration of the experimental rats compared with the control animals was observed 6 and 10 months after the beginning of the experiment (Fig. 2).

During the action of acute stress on the rats of the experimental and control groups in the period when the blood corticosterone level of the animals receiving [^{75}Se] selenomethionine reached its highest value, the

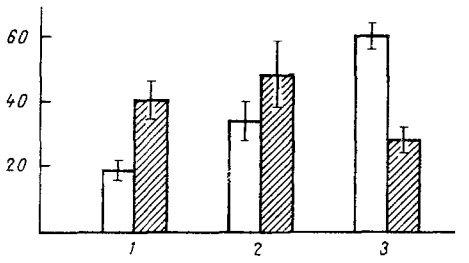

Fig. 3. Corticosterone concentration in plasma of control animals poisoned with [^{75}Se] selenomethionine and in stressed rats. Ordinate, cortisol concentration (in ng/100 ml); 1) unstressed animals; 2) stress induced by injection of histamine 30 min before sacrifice; 3) stress induced by injection of formalin 30 min before sacrifice. Unshaded columns show plasma cortisol level of control animals, shaded columns show plasma cortisol level in animals receiving [^{75}Se] selenomethionine.

following pattern was revealed. The hormone concentration in the plasma rose sharply in the control animals 30 min after the development of acute stress induced by injection of histamine or formalin, as might be expected, whereas no such response developed in the rats receiving the radioactive preparation (Fig. 3). After injection of formalin, incidentally, the plasma corticosterone concentration in the animals of the experimental group was somewhat lower than that in the rats of the same group not exposed to stress.

The rise in the plasma corticosterone level in the late stages after absorption of small doses of [^{75}Se]-selenomethionine thus indicates that a radiation load not exceeding 10 rad is not without its effect on the functional state of the pituitary–adrenal system. In this connection interesting results were obtained by Kandror, who showed that the threshold dose for the response of the adrenals to internal irradiation (^{24}Na) is even lower when changes in the ascorbic acid concentration are used as the criterion, namely 0.7-1.6 rad [7]. Under the present experimental conditions when the concentration of [^{75}Se] selenomethionine in the endocrine organs was considerably higher than that in the body as a whole, the radiation load on this system was possibly higher than the mean. Moreover, it must be remembered that the irregularity of distribution of [^{75}Se] selenomethionine within the same organ, tissue, and even cell, due to the presence of soft electron radiation in its spectrum [15], with short mean paths of the particles and with an ionization density of the same order as that of α-particles [18], may lead to the formation of higher than mean values of local absorbed doses and, consequently, to a more marked biological effect than in the case of uniform irradiation. The biological effect of [^{75}Se] selenomethionine observed in these experiments in the adaptation system is evidence not only of a change in the function of that system, but also of its inability to respond adequately to the action of extremal factors and, in particular, to pharmacological stress. The additional stressor loads showed that the high functional activity of the adaptation system in these experiments were nothing more than extreme stress of that system. Consequently, the compensatory and adaptive powers of animals receiving a single dose of [^{75}Se] selenomethionine were considerably depressed. It can be postulated on the basis of these facts that analysis of the functional state of the adaptation system could provide the key to the assessment of the biological effect of small doses of radiation.

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