EFFECT OF INCORPORATED ^{131}I ON ELECTRICAL AND BIOMECHANICAL ACTIVITY OF THE HEART AND CORONARY BLOOD FLOW AND THEIR ADRENERGIC REGULATION

A. E. Kirienko, N. N. Petrashevskaya, and L. M. Lobanok

UDC 577.391

KEY WORDS: heart; adrenoreceptors; radionuclides.

An essential role in the pathogenesis of radiation damage to cells, organs, and systems is played by effects mediated through neurohumoral mechanisms [2, 6]. In particular, certain postradiation changes of cardiac function are based on disturbances at different levels of its adrenergic regulation [3, 14]. At the present time, in connection with radiation contamination of the environment, particular importance is attached to the study of biological effects of incorporated radionuclides, among which (as was the case, for example, are the Chernobyl' Atomic Power Station disaster) isotopes of iodine may be very important.

The aim of this investigation was to study the immediate and late effects of incorporated ^{131}I on electrical and biomechanical activity of the heart and on their adrenergic regulation.

EXPERIMENTAL METHOD

Experiments were carried out on mature female Wistar rats aged 6, 9, 12, and 18 months and weighing 210 ± 5, 262 ± 6, 296 ± 8, and 332 ± 11 g respectively. At the age of 5 months the animals were given a single intraperitoneal injection of ^{131}I in a dose of 2.5 MBq/kg, the body level of which was determined on a "Nokia P4900B" programmed multichannel analyzer (Finland). Dose loads were calculated by equations in [5]. The absorbed dose in the thyroid gland was 94.6 Gy during the 1st month and 94.7 Gy during 12 months. The animals were anesthetized with thiopental sodium (80 mg/kg). Experiments were carried out on the isolated perfused heart [4] and on preparations of the right atrium with intact sinus node. Intracellular electrical activity of right atrial cardiomyocytes was recorded by the standard microelectrode technique ("Experimetria," Hungary), using floating microelectrodes with a resistance of 20-30 MΩ. Phenylephrine (10^{-7}-10^{-4} M) was used to stimulate α-adrenoreceptors. Isoprenaline (VEB Berlin-Chemie, East Germany) in concentrations of 10^{-9}-10^{-5} M was used as β-receptor agonist. The following parameters were recorded: heart rate (HR, beats/min), maximal systolic (P_{max}, mm Hg) and diastolic (P_{min}, mm Hg) pressures, rate of rise ($+dP/dt_{max}$, mm Hg/sec) and fall ($-dP/dt_{max}$, mm Hg/sec) of intraventricular pressure, volume velocity of the coronary blood flow (VVCF), resting potential (RP, mV), amplitude of the action potential (AP, mV), frequency of spontaneous activity (AP/sec), duration of AP at 90 and 50% of repolarization levels (DAP_{90} and DAP_{50} respectively, msec). Body mass (BM), mass of the heart (MH) and left ventricle (MLV), and the ratios MH/BM and MLV/BM were measured and calculated. The results were subjected to analysis by IBM PC/AT personal computer.

EXPERIMENTAL RESULTS

As Table 1 shows, 1 month after injection of ^{131}I, VVCF was reduced, but after 3 months the heart rate was increased. After 6 months these parameters of cardiac function of animals with incorporated ^{131}I did not differ

Laboratory of Physiology, Institute of Radiobiology, Academy of Sciences of Belarus'. (Presented by Academician of the Russian Academy of Medical Sciences V. A. Matyukhin.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 114, No. 10, pp. 340-343, October, 1992. Original article submitted March 24, 1992.

 0007-4888/92/0010-1390$12.50

TABLE 1. Effect of Incorporated ^{131}I on Functional Characteristics of Isolated Heart and Myocardial Preparations ($X \pm S_{\bar{x}}$)

Postradiation period	Parameter					
	P_{max}, mm Hg	VVCF, ml/min	HR, beats/min	RP, mV	AP, mV	DAP_{90}, msec
Control	68,0±4,3	9,2±0,3	253,1±4,8	67,2±3,3	82,1±8,3	40,6±2,8
1 Month	73,6±3,8	7,4±0,3	257,9±5,9	70,5±5,6	85,6±7,0	46,0±3,1
3 Months	74,8±3,6	6,3±0,1*	271,4±5,2*	69,7±6,6	80,2±7,3	52,0±5,5
6 Months	83,6±4,5	8,1±0,5	244,0±5,1	66,4±4,4	82,6±6,9	35,7±4,5
12 Months	90,9±2,8*	9,6±0,5	253,5±4,9	64,4±6,8	88,5±8,1	57,0±2,9*

Legend. *$p < 0.05$ Indicates significant differences from control.

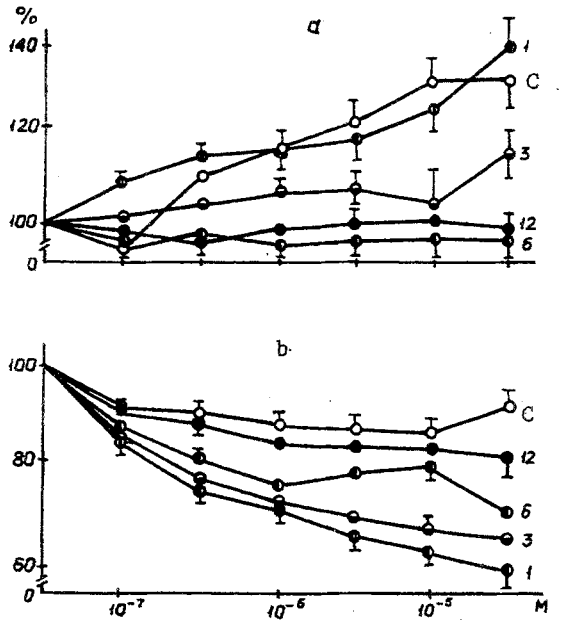

Fig. 1. Effect of phenylephrine on rate of relaxation of isolated heart (a) and volume velocity of coronary blood flow (b) in animals with incorporated ^{131}I. Abscissa, concentration of agonist (in M); ordinate, values of parameters (percentages of initial level), 1, 3, 6, 12) Months after injection of radionuclide; C) control.

significantly from those in the control experiments, but toward the 12th month of the observations the pressure developed by the left ventricle increased, and the rate of its rise and fall increased by 34, 32, and 50% respectively. The equal ratio of the mass of the heart to body mass ($4.2 \cdot 10^{-3}$ in the control, $4.1 \cdot 10^{-3}$ in the experiment) and of the mass of the left ventricle to body mass ($2.8 \cdot 10^{-3}$ and $2.7 \cdot 10^{-3}$ respectively) indicated absence of myocardial hypertrophy in the experimental animals. Values of resting potential and action potential in animals with incorporated ^{131}I in the early periods did not differ from the control values, but by the 12th month after injection of the radionuclides an increase in DAP_{90} was recorded (Table 1), a phenomenon known to take place when activity of electrogenic Na-Ca-exchange in the myocardial cells is increased [13]. Reliable recovery P_{max} for that period conformed with available literature data dealing with a decided link between DAP_{90} and amplitude contraction response.

Stimulation of α-adrenoreceptors did not change the rhythmic activity of the heart of animals of the control group but strengthened myocardial contractions and caused a small (by 13%) decrease in coronary flow, HR of rats with incorporated ^{131}I likewise was unchanged in response to the action of phenylephrine, but the inotropic response was reduced by 20-37% ($p < 0.01$, Fig. 1a). The response of the coronary vessels to the α-adrenergic agonist 30

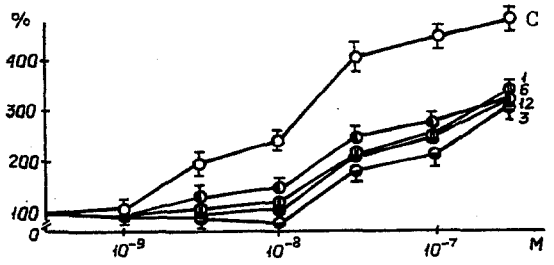

Fig. 2

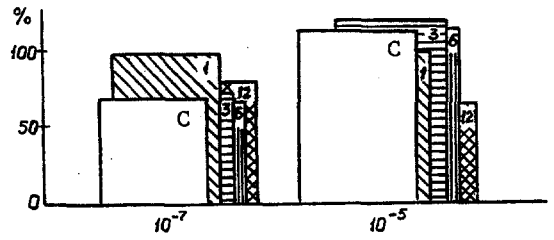

Fig. 3

Fig. 2. Dynamics of rate of relaxation of isolated heart of rats with incorporated ^{131}I during β-adrenoreceptor stimulation by isoprenaline. Legend as to Fig. 1.

Fig 3. Effect of isoprenaline on DAP_{90} of right atrial cardiomyocytes of rats in immediate and late stages after injection of ^{131}I. Legend as to Fig. 1.

days after injection of ^{131}I was increased by 40%, but after 1 year it did not differ significantly from the control value (Fig. 1b).

Cardiomyocytes of the right atrium responded to α-adrenoreceptor stimulation of the control animals by depolarization, an increase in the frequency of AP, and reduction of their temporal parameters, in agreement with data in the literature on the ability of α-adrenergic agonists to potentiate the calcium current through activation of protein kinase C [11]. In the early periods (1 month) after injection of ^{131}I phenylephrine had no electrophysiological effects. During the next 3-6 months the response of the cells to this agonist was restored, and after 1 year an increase in sensitivity and strengthening of the functional response of the cardiomyocytes to its action were recorded. In particular, the frequency of AP in the control experiments, with the agonists in a concentration of 10^{-5} M, was increased by 30%, whereas in experiments on atrial preparations of animals with incorporated ^{131}I it was increased by 83% ($p < 0.01$).

In rats subjected to the action of the radionuclide the response of the heart to β-adrenoreceptor stimulation also changed and was not restored after 1 year. For instance, 1 month after injection the maximal chronotropic effect observed with isoprenoline in the perfusion solution in a concentration of 10^{-6} M was reduced by 11% ($p < 0.05$), whereas that of the inotropic effect, assessed by the change in intraventricular pressure, and the rates of its rise and fall was reduced by 60-155% ($p < 0.001$, Fig. 2), and the response of the coronary vessels was reduced by 20% ($p < 0.01$). Weakening of the functional response also took place under the influence of low concentrations of the agonist ($5 \cdot 10^{-9}$ M): for instance, $-dP/dt_{max}$ in the control increased by 209% but in the experiment by only 107% ($p < 0.001$). Changes of this kind also were characteristic of the time course of HR and VVCF.

The functional response of cardiomyocytes of the control animals to β-adrenoreceptor stimulation consisted of membrane depolarization and an increase in the frequency and amplitude of AP. An increase in DAP_{90} (by 25%) against the background of an increase in frequency of AP (by 35%), recorded in response to isoprenaline 10^{-5} M, indicates compensatory activation of the Na–Ca ion-exchange mechanism, preventing calcium overloading of the cells and lengthening the refractory phase (Fig. 3). There was no response to β-receptor stimulation 30 days after the beginning of exposure to radiation. Later (after 3-12 months) electrophysiological effects of isoprenaline characteristic of intact animals were recorded, but their magnitude, estimated in particular from the change in frequency of spontaneous activity, was depressed by 15% ($p < 0.05$). Moreover, higher concentrations of the agonist (10^{-5} M), unlike in the control, led to reduction of DAP_{90} by 32%, evidence at least of the absence of any increase in Na–Ca exchange activity in response to β-adrenergic influences, and it may be one cause of weakening of the inotropic reaction of the isolated heart of animals with incorporated ^{131}I to isoprenaline.

Adrenergic regulation of electrical and biomechanical functions of the heart is thus essentially modified by the action of incorporated ^{131}I. This is shown, in particular, by the marked weakening of the effect of β-adrenoreceptor stimulation on myocardial function. So far as α-adrenergic structures are concerned, the response of the coronary blood flow to their stimulation, on the contrary, was increased. The electrical response of the cardiomyocytes to α-adrenergic agonists also increased in the late stages, after initial inhibition immediately after injection of ^{131}I. The mechanisms of modification of adrenergic control may consist of desensitization of receptor structures on account of disturbance of coupling with adenylate cyclase and reduction of their density and affinity for agonists, as is shown by data obtained by other workers on models with radiation-induced and other forms of myocardial damage [6, 8, 10]. These must include possible changes in the system of transsarcolemmal transport of Ca^{2+}, which controls the slow, late phase of the action potential plateau. In the present investigation, regulatory changes arising in response to injection of ^{131}I were evidently mediated through thyroid hypofunction, which invariably arises when the absorbed dose of γ-radiation formed on it is 10 Gy [15]. There are two aspects to these results. First, they are evidence of the possibility of opposite changes in structural and functional properties of the adrenergic receptors involved in the regulation of the chronotropic and iontropic functions of the heart and coronary vascular tone, and they are in agreement with results obtained in other experimental situations, notably hypokinesia, hyperkinesia, etc. [1]. Second, weakening of the response of the myocardium to β-adrenoreceptor stimulation, accompanied or not by its strengthening in response to α-adrenoreceptor stimulation, takes place in many pathological states such as hypertension, hypothyroidism, hypothermia, heart failure, aging, and the response of the body to external γ-irradiation [7-9]. This regulatory modification is thus a nonspecific response of the body and is evidence of the development of a prepathological state of the heart.

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