PHYSIOLOGY

Chronic Administration of Interferon-α Decreases Blood Pressure and Heart Rate in Rats

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We studied the effects of interferon-α on rat cardiovascular system. Intravenous administration of intron-A in a dose of 100,000 IU/kg for 3 days led to a permanent and statistically significant decrease in blood pressure (on days 2 and 3) and reduction in heart rate. These effects were not associated with changes in baroreflex regulation of the cardiovascular system.

Key Words: *interferon-α; baroreflex; blood pressure*

Interferons play an important role in viral infections, tumors, and other diseases associated with the presence of foreign nucleic acid molecules or structural damages to nucleic acids. Interferons are widely used for the therapy of various tumors and severe viral diseases. Therefore, the physiological role and consequences of their use are of considerable importance. Under normal conditions, plasma interferon concentration is below 4 IU/ml (10^{-12} M). In severe diseases, this parameter increases to 100 IU/ml, while the ability of interferon-producing cells to secrete interferons decreases. Therapeutic doses of interferons and administration route depend on the type and severity of the disease. In severe leukemia and during remission, interferon is used in daily doses of 200,000 and 10,000 IU/kg, respectively. Interferon preparations cause various side effects, including nausea, dizziness, and blood pressure (BP) variability [1,2]. However, the effects of these preparations on the cardiovascular system received little attention. Here we studied the effects of daily administration (for 3 days) of intron-A (interferon-α) on BP, heart rate (HR), and variability of these parameters in alert rats.

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MATERIALS AND METHODS

Experiments were performed on male Wistar rats weighing 287.3±18.8 and 285.8±17.1 g (control and treated animals, respectively). Two days before the experiment, polyethylene catheters were implanted into the femoral artery (PE 10) and jugular vein (PE 50) for recording BP and HR and infusion of preparations, respectively. Intron-A in a dose of 100,000 IU/kg (15 ml) was administered intravenously in a bolus. Control animals received an equivalent volume of 0.9% NaCl. Sodium nitroprusside (SN) in a dose of 4 μg/kg and phenylephrine (PE) in a dose of 2 μg/kg (20 μl) were used to estimate the baroreflex sensitivity. Catheters were washed with 50 μl 0.9% NaCl.

The experiments were conducted for 3 days by the same schedule: SN was administered 1 h after the start of experiment, PE and intron-A (or 0.9% NaCl) were then infused at 15-min intervals, SN was introduced again 1 h after administration of intron-A, and 15 min later, the animals were injected with PE. The observations were completed 15 min after the last injection. BP and HR were recorded in awake freely moving rats. The arterial catheter was connected to a Statham

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TABLE 1. Initial BP, HR, and Their Variability and BP Response to NP and PE in Wistar Rats Treated with Intron-A (*M±m*)

Parameter	Day					
	1		2		3	
	control	experiment	control	experiment	control	experiment
BP, mm Hg	127.6±2.8	122.4±4.0	126.5±3.7	113.3±2.9**	119.3±5.2	109.7±3.5*
HR, bpm	347.0±7.2	360.2±13.4	334.6±11.2	342.0±15.9	334.4±8.8	328.5±10.4**
BP variability, mm Hg	5.0±0.4	5.1±0.3	5.6±0.4	5.0±0.4	5.0±0.4	4.2±0.3
HR variability, bpm	42.4±9.0	33.7±3.6	39.8±5.6	37.3±4.7	39.9±6.4	43.8±5.5**
BP changes, mm Hg:						
SN	-25.4±3.5	-22.5±2.6	-28.5±5.4	-24.7±2.5	-23.8±3.2	-25.3±1.9
PE	29.6±2.4	23.3±3.8	28.9±4.6	32.9±3.9	27.5±3.5	34.9±3.8**

Note. *$p<0.01$ and **$p<0.05$ compared to day 1.

pressure transducer; the venous catheter was connected to a syringe (via an adapter) with test substances. The rats were adapted to experimental conditions for at least 1 h. The experiment was started at 9 a.m. The control and experimental rats were examined simultaneously. The results were recorded using ZAI software, which allowed us to evaluate BP, HR, and variability of these parameters calculated as their standard deviation on the studied curve segment.

Changes in BP, HR, and variability of these parameters were recorded for 3 days (1 h a day). The effect of intron-A or 0.9% NaCl on the recorded parameters was then analyzed. Physiological parameters estimated over a 15-min interval were then averaged. The baroreflex coefficient was calculated as the ratio between changes in the pulse interval and BP (msec/mm Hg) in response to administration of SN and PE. The results were analyzed by Student's *t* test. The differences were significant at $p<0.05$. We performed 8 experiments on control rats and 8 experiments on treated rats.

RESULTS

The initial BP did not significantly differ in treated and control rats (122.4±4.0 and 127.6±2.8 mm Hg, respectively). BP in treated rats progressively decreased by 9.1 ($p<0.05$) and 12.7 mm Hg ($p<0.01$) on days 2 and 3, respectively, compared to the initial level. In control animals, BP did not significantly change over 3 days (Table 1). These findings are consistent with clinical studies on patients receiving immunotherapy [2-4,6].

During the 1st day, HR was similar in control and treated rats 347.0±7.2 and 360.2±13.4 bpm, respectively). On day 3, HR in treated rats decreased by 98% ($p<0.05$) compared to that on day 1 (Table 1).

This decrease in HR against the background of BP drop on day 3 can be due to the inhibition of baroreflex mechanisms regulating systemic BP and negative chronotropic effects of intron-A.

Our experiments showed that the baroreflex is not involved in the realization of interferon-induced effects on BP and HR. The baroreflex coefficient in response to SN and PE in treated rats did not change from the control (Table 2). Similar regularities were reported by M. Fukuhara *et al.* [5], who analyzed *R-R* intervals and BP changes during the therapy of chronic hepatitis [5]. At the same time, BP response to PE in treated rats was enhanced by 9.6 and 11.6 mm Hg ($p<0.05$) on day 2 and 3, respectively, compared to the

TABLE 2. Changes in Baroreflex Coefficient (msec/mm Hg) Induced by SN and PE after Administration of Intron-A (*M±m*, *n*=8)

Day		Before intron-A administration		After intron-A administration	
		control	experiment	control	experiment
1	SN	1.3±0.1	1.7±0.2	0.9±0.2	1.3±0.2
	PE	1.4±0.3	1.2±0.3	0.9±0.2	1.5±0.1
2	SN	1.6±0.3	1.4±0.3	1.4±0.2	1.5±0.4
	PE	1.8±0.2	1.3±0.3	1.8±0.6	1.3±0.3
3	SN	1.2±0.3	1.5±0.4	1.7±0.6	1.4±0.3
	PE	1.3±0.2	0.9±0.2	1.1±0.1	1.5±0.4

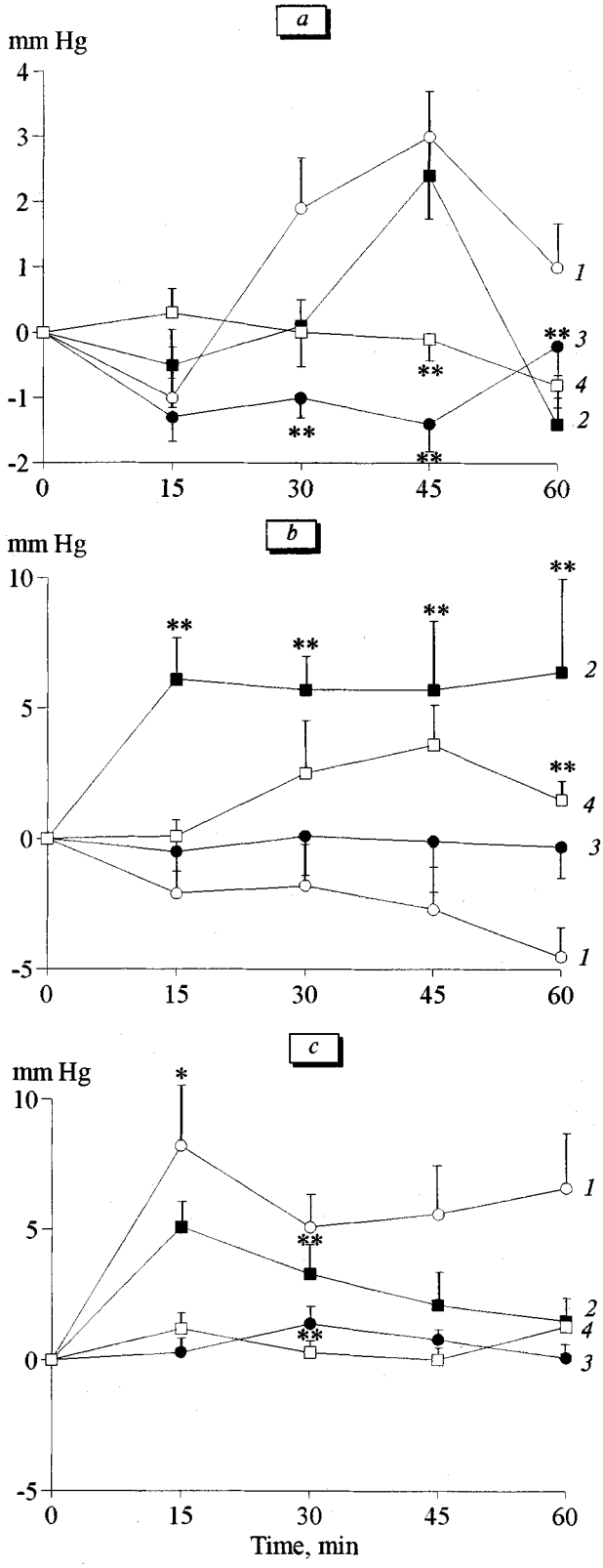

Fig. 1. Changes in BP (*1*, *2*) and BP variability (*3*, *4*) 1 h after administration of intron-A on days 1 (*a*), 2 (*b*), and 3 (*c*) of observations. Here and in Fig. 2: control (*1*, *3*) and experiment (*2*, *4*). *$p<0.01$ and **$p<0.05$ compared to the initial level.

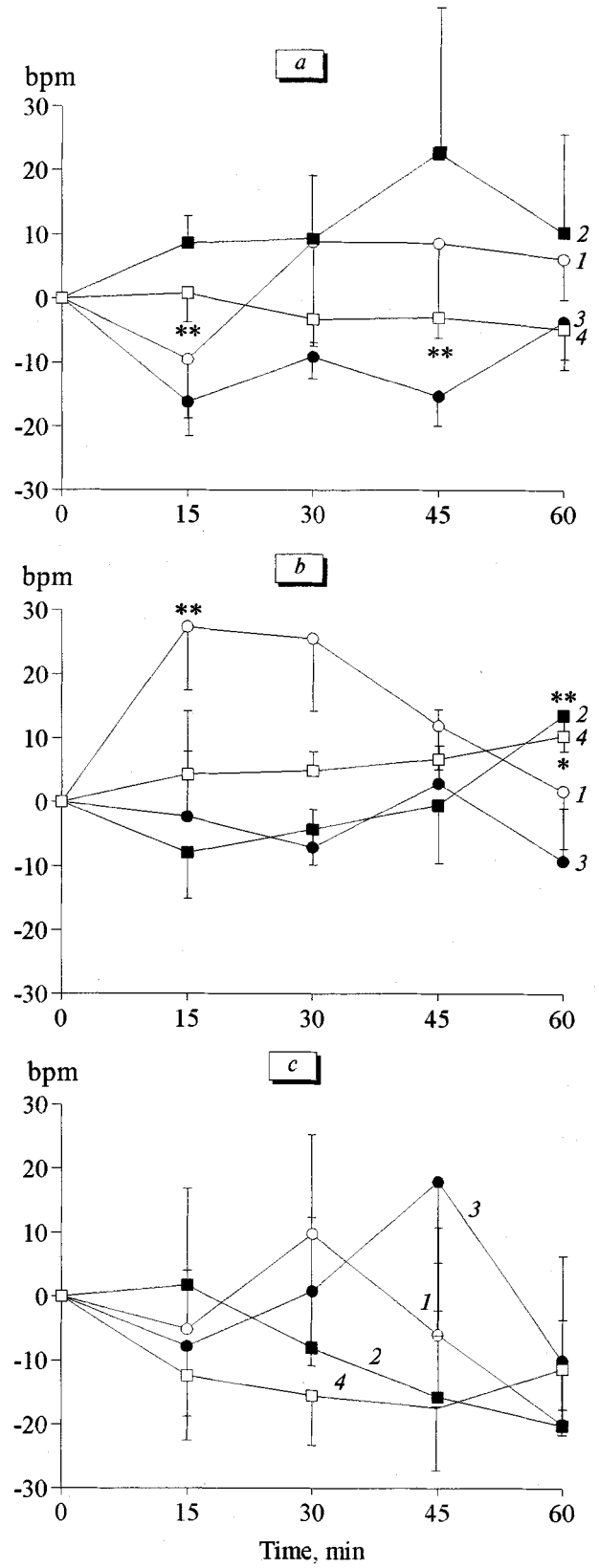

Fig. 2. Changes in HR (*1*, *2*) and HR variability (*3*, *4*) 1 h after administration of intron-A on days 1 (*a*), 2 (*b*), and 3 (*c*) of observations.

initial reaction, while the response to SN remained unchanged (Table 1). This reaction against the background of reduced BP and HR observed on day 3 of therapy indicates an imbalance in the regulation of heart activity and vascular resistance. The enhanced response to PE reflects increased reactivity of vascular smooth muscles to vasoconstrictors. The reduction in BP probably results from decreased blood concentrations of vasoconstrictors or reflects the secondary reaction associated with direct influence of intron-A on the heart (negative chronotropic effect).

Changes observed 1 h after administration of intron-A were different on days 1, 2, and 3. On day 1, the preparation slightly increased HR, but did not change BP and variability of these parameters (Figs. 1, *a*, and 2, *a*). On day 2, intron-A significantly elevated BP and HR; the variability of BP and HR tended to increase (Figs. 1, *b*, and 2, *b*). Previous studies showed that high doses of interferon-α increase vascular resistance in some regions [6]. On day 3, intron-A produced the following effects: HR tended to decrease, BP remained practically unchanged, and HR variability was reduced by 15.1 bpm ($p<0.01$) over the last 45 min of observations (Figs. 1, *c*, and 2, *c*). These data confirm that intron-A produces negative chronotropic effects. Our findings suggest that the preparation can modulate heart activity.

In conclusion, intravenous administration of 100,000 IU/kg intron-A for 3 days led to a permanent and statistically significant decrease in BP and HR reduction. These reactions were not associated with changes in baroreflex regulation of the cardiovascular system. Hence, intron-A is involved in the regulation of the cardiovascular system.

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