PHARMACOLOGY AND TOXICOLOGY

Hemodynamic Effects of Tetrindol in Alert Normotensive Mice and Rats after Blockade of Nitric Oxide Synthesis

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Single intravenous injection of antidepressant tetrindol (1 and 10 mg/kg), a reversible monoamine oxidase A inhibitor, dose-dependently decreased heart rate and mean arterial pressure (in a concentration of 10 mg/kg) in alert NMRI mice and Sprague-Dawley rats. Nitric oxide synthase blockade with L-NAME attenuated tetrindol-induced bradycardia in rats and completely abolished this effect in mice.

Key Words: *antidepressants; tetrindol; hemodynamics; nitric oxide*

Previous studies showed that antidepressant tetrindol (TI) decreases heart rate (HR) in narcotized Wistar rats [1]. This effect persisted even after pharmacological cardiac denervation, which suggests direct action of TI on the heart. Nitric oxide (NO) is synthesized in various structures of the heart [3,4] and plays an important role not only in the modulation of parasympathetic effects on HR [2,6], but also in functioning of cardiomyocytes, conduction system, and coronary vessels [3, 4]. The mechanism of TI-induced bradycardia is still unclear. At the same time, the preparations decreasing HR attract much attention in the development of new approaches to the therapy of cardiovascular diseases [5].

Here we studied hemodynamic effects of TI in alert mice and rats against the background of NO synthase blockade with L-NAME.

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MATERIALS AND METHODS

Experiments were performed on male NMRI mice and Sprague-Dawley rats weighing 40-46 and 420-480 g, respectively (Institute of Bioorganic Chemistry). The animals were kept under standard conditions at 22± 2°C, 12-h light-dark regimen (daytime 8.00-20.00), and *ad libitum* food and water supply.

One day before the experiment, the mice were intramuscularly narcotized with 3 mg/kg droperidol and 63 mg/kg calipsol (Gedeon Richter). Polyethylene catheters were introduced via the left carotid artery into the thoracic aorta for recording blood pressure (BP) and into the left jugular vein for infusion of test drugs. Peripheral ends of the catheters were passed under the skin and fixed in the interscapular area. The rats were intraperitoneally narcotized with 100 mg/kg calipsol 1 day before the experiment. Polyethylene catheters were introduced via the femoral artery into the abdominal aorta for recording BP and into the femoral vein for administering substances.

BP was measured by an electrical manometer. The BP curve was plotted using a computer, and the mean BP and HR were calculated.

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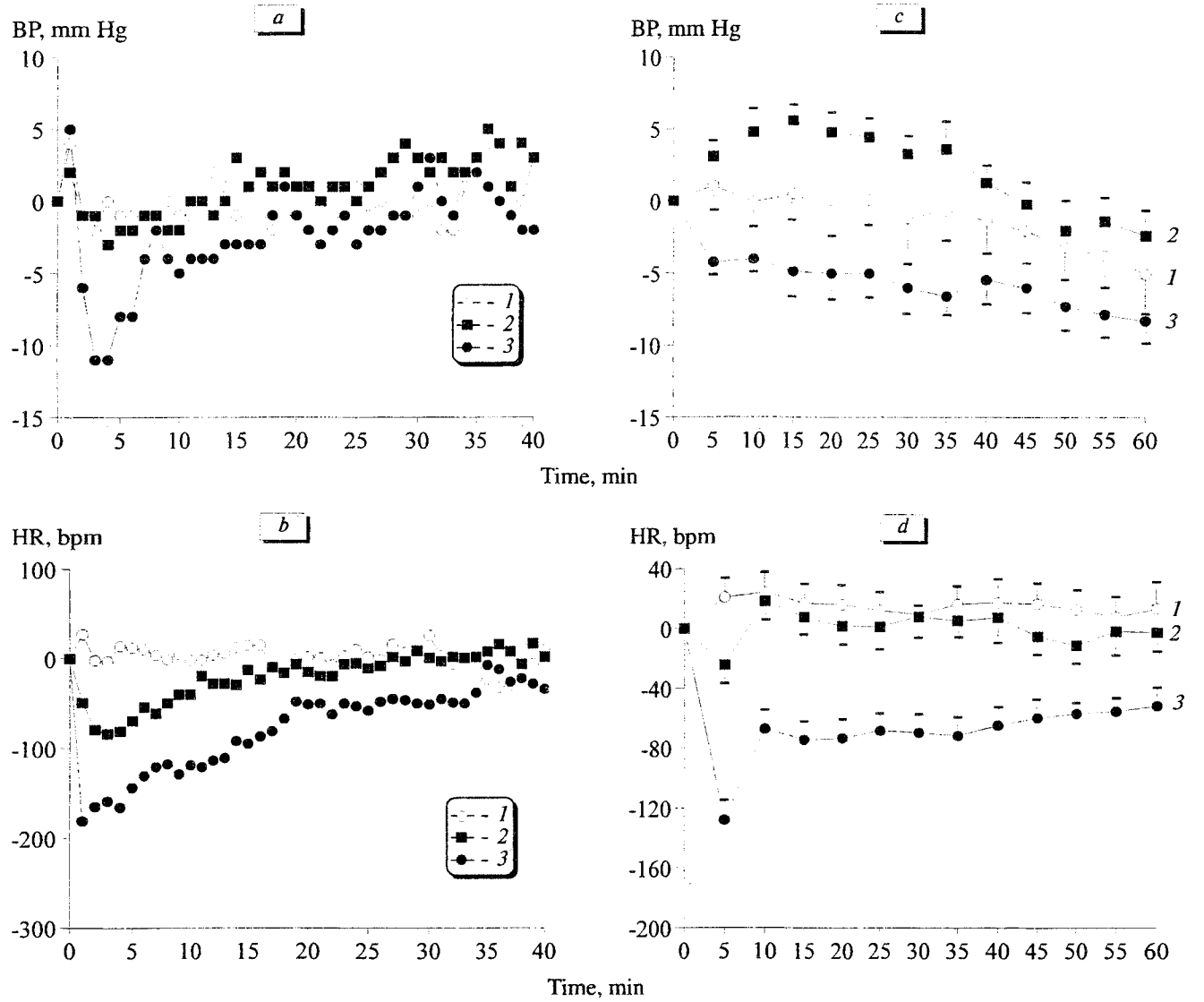

Fig. 1. Changes in blood pressure (BP, *a*, *c*) and HR (*b*, *d*) in normotensive mice (*a*, *b*) and rats (*c*, *d*) induced by intravenous injection of tetrindol in doses of 1 (*2*) and 10 mg/kg (*3*) compared to the control (*1*).

TABLE 1. Initial Parameters of Hemodynamics in Alert Normotensive Mice and Rats ($M \pm m$, n=6-7)

Parameter	Series I			Series II			
	control	TI, mg/kg		before L-NAME administration		after L-NAME administration	
		1	10	control	TI, 10 mg/kg	control	TI, 10 mg/kg
Mean BP, mm Hg							
mice	121±8	119±6	125±6	120±3	126±4	145±2	151±6
rats	120±3	111±4	115±2	112±4	113±1	141±3	135±2
HR, bpm							
mice	460±51	517±44	497±54	488±51	435±27	324±17	296±14
rats	342±19	331±17	337±12	319±3	345±12	263±6	283±8

TABLE 2. TI-Produced Changes in HR (bpm) before and after Blockade of NO Synthase

Experimental conditions	Control	TI, mg/kg	
		1	10
Before L-NAME administration			
mice	-2	-84*	-181*
rats	21	-25*	-128*
After L-NAME administration			
mice	27	0	3+
rats	11	0	-60*+

Note. $p<0.05$: *compared to the control, +compared to HR before blockade.

In series I, dose-dependent hemodynamic effects of single intravenous injection of TI (1 and 10 mg/kg) were studied in mice and rats. Control animals were injected with Tween 80 (Sigma) in 0.9% NaCl. Hemodynamic parameters were monitored for 40-60 min postinjection.

In series II, we studied hemodynamic effects of 10 mg/kg TI injected intravenously to mice and rats 10 min after intravenous administration of 100 mg/kg Nω-nitro-L-arginine methyl ester (NO synthase blocker, L-NAME, Sigma). Control animals received the solvent.

The results were analyzed using Duncan two-way rank test. The differences were significant at $p<0.05$.

RESULTS

The initial BP and HR did not significantly differ between control and experimental mice and rats in each experimental series (Table 1).

In series I, TI in a dose of 10 mg/kg decreased BP in mice. Maximum decrease in BP was observed 4 min postinjection (by 11±4 mm Hg, Fig. 1, *a*), while the decrease in HR was noted 3 and 1 min after administration of 1 (by 84±19 bpm) and 10 mg/kg TI (by 181±47 bpm), respectively (Fig. 1, *b*). The dose-dependent bradycardic effects of TI lasted 10 and 30 min, respectively ($p<0.05$ compared to the control).

BP in rats decreased by 6-8 mm Hg under the effect of 10 mg/kg TI, but increased by 5-6 mm Hg after injection of 1 mg/kg TI (Fig. 1, *c*). The maximum decrease in HR was observed 5 min after injection of 1 (by 24±8 bmp) and 10 mg/kg TI (by 128±12 bpm, Fig. 1, *d*). The bradycardic effect of 1 mg/kg TI were statistically significant over the first 10 min postinjection ($p<0.05$ compared to the control). The effects of TI in a dose of 10 mg/kg differed (statistically significantly) from those of 1 mg/kg TI and from the control over 60 min of observations.

In series II, L-NAME increased BP and decreased HR in mice and rats (Table 1). Under conditions of NO synthase blockade, TI had no effect on BP in mice and rats. Furthermore, in a dose of 10 mg/kg TI caused no bradycardia in mice and produced less pronounced changes in HR in rats (Table 2).

Hence, TI caused bradycardia in rats and, to a greater degree, in mice. Blockade of NO synthase completely abolished TI-induced bradycardia in mice and attenuated this effect in rats (by 50%). These data indicate the involvement of NO in TI-induced bradycardia.

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