Cardiac Output in Rats of Different Ages during Blockade of α_1 and β-Adrenoceptors

R. R. Nigmatullina, R. A. Abzalov, and E. Sh. Minnibaev

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 127, No. 6, pp. 638-641, June, 1999
Original article submitted February 22, 1999

In acute experiments on rats of different ages (21, 30, 42, and 70 days), the α_1-adrenoblocker prazosin increased the heart rate (HR), and the β-blocker propranolol (Obsidan) infused after prazosin reduced this parameter. Prazosin decreased both stroke volume and cardiac output, blockade of β-adrenoceptors further decreased these parameters. It is concluded that both α_1- and β-adrenoceptors are involved in the sympathetic regulation of cardiac output in developing animals.

Key Words: α_1- *and* β-*adrenoceptors; prazosin; stroke volume; developing rats; heart rate*

Adrenergic regulation of chronotropic and contractile cardiac functions is known to be mediated by α_1- and β-adrenoceptors (AR) [4,6,9]. Atrial and ventricular cardiomyocytes in rats express different α_1-AR subtypes [10-12,16]. In rat heart, the positive inotropic effect of epinephrine is realized primarily via α_1B-AR through modulation intracellular Ca^{2+} concentration [12]. The ratio for A and B subtypes of α_1-AR in rat heart is 20:80 [15]. Sustained positive inotropic effects of α_1-agonists on the atria and ventricles in rat heart are mediated by activation of both α_1-AR subtypes of [15]. Several studies investigated the role of β-AR in the regulation of stroke volume (SV), cardiac output (CO) and heart rate (HR) in the developing organism [1,2,4,5]. At the same time, the role of α_1-AR in *in vivo* regulation remained little studied and was the subject of our study.

MATERIALS AND METHODS

Experiments were carried out on outbred albino rats at the age of 21, 30, 42, and 70 days. Stroke volume was measured by a modified technique of tetrapolar chest rheography [1,3,8]. Differential rheogram was recorded by an RPG-204 apparatus in animals anesthetized with Nembutal (40 mg/kg) under conditions of natural ventilation. Cardiac output was calculated from SV and HR. Prazosin (10^{-7} mol/liter) in a dose of 0.17 mg/100 g and propranol (Obsidan, 0.1% solution) in a dose of 0.8 mg/100 g were used. The drugs were infused through a catheter into the jugular vein. The second drug was administered after the changes in HR induced by the first preparation attained the maximum.

In series I, AR were blocked first with propranolol and then with prazosin; in series II the order of infusions was inverted.

The data were analyzed statistically using Student's *t* test.

RESULTS

Through the period from 21 to 70 days of life SV in rats increased 3.8 times (Table 1). In 21-day-old rats, propranolol reduced SV and subsequent infusion of prazosin further decreased this parameter. Similar changes were observed in rats of all age groups (Table 1).

Series II with inverse order of administration gave similar results (Table 1).

In series I, HR increased from day 21 to 30 and then decreased by the 70th day (Table 2). Propranolol reduced HR in 21-day-old rats, while in adult animals (70-day-old) the reaction was less pronounced. Under

Kasan' State Pedagogical University; Kasan State Agricultural Academy

0007-4888/99/0006-0580$22.00

these conditions, the blockade of α_1-AR with prazosin further reduced HR in young and adult rats by 49 and 29 beats/min, respectively.

In series II, prazosin increased HR in both 21- and 70-day-old rats, while propranolol decreased it (Table 2). CO in rats of series I increased by the 70th day of life (Table 3). In 21-day-old rats, the blockade of β-AR reduced the CO by half and the following blockade of α_1-AR further reduced it by 45.6%. In 30-, 42- and 70-day-old animals the responses to propranolol and prazosin were less pronounced.

Similar changes in CO were observed in series II (Table 3).

In series II, infusion of the α_1-adrenoblocker prazosin accelerated HR. This response can be considered as a reflectory reaction to prazosin-induced vasodilation and a decrease in blood pressure. The HR was lowered by subsequent administration of propranolol. These changes can be explained as follows: after blockade of α_1-AR the presynaptic AR continued to stimulate the release of norepinephrine into the synaptic cleft, and since blocked postsynaptic α_1-AR were insensitive to catecholamines, the accumulating transmitter more intensely interacted with β-AR, which induced the rise of HR.

Propranolol is a nonselective β-antagonist that blocks both pre- and postsynaptic β-AR. Therefore, the blockade of β-AR reduces the concentration of transmitter in the synaptic cleft through the positive feedback mechanism. Propranolol caused changes in CO typical for the blockade of β-AR. Under these conditions, prazosin blocks the postsynaptic α_1-AR and caused further decrease in SV, CO and HR.

Our data showed that in 21-day-old rats the sympathetic influences on HR are mediated primarily by propranolol-sensitive receptors and the reaction of HR to the blockade of α_1-AR is less pronounced. At this age, the sympathetic influences on HR were found to be much stronger than parasympathetic, which explains the higher values of HR [1,2,5,6]. In 42-day-

TABLE 1. Stroke Volume (ml×10^3) in Rat Pups after Consecutive Blockade of β- and α_1-Adrenoceptors (*M±m*)

Experimental conditions	Age, days			
	21 (*n*=17)	30 (*n*=15)	42 (*n*=10)	70 (*n*=11)
Series I				
Initial values	58±1.7	75±3.6	116±5	221±1.3
After administration of propranolol	43±1.9***	47±3.3***	63±6***	133±1.1***
prazosin	27±2.6+++	37±2.7+++	37±4.1++	101±0.9+++
Series II				
Initial values	48±3.8	80±7.2	122±9.4	181±16
After administration of prazosin	32±2.6***	63±0.8*	79±9**	94±14**
propranolol	22±2.8+++	39±7.5+	53±6.6+	56±6+

Note. Here and in Tables 2 and 3: *$p<0.05$, **$p<0.01$, ***$p<0.001$, compared with the initial values; +$p<0.05$, ++$p<0.01$, +++$p<0.001$, compared with previously administered drug.

TABLE 2. Heart Rate (beats/min) in Rat Pups after Consecutive Blockade of β- and α_1-Adrenoceptors (*M±m*)

Experimental conditions	Age, days			
	21	30	42	70
Series I				
Number of rats	10	11	10	10
Initial values	461.94±9.29	466.94±6.78	442.14±9.49	424.00±6.24
After administration of propranolol	332.02±8.60***	349.18±8.22***	357.92±8.82***	336.30±9.60***
prazosin	283.28±19.33+	310.89±15.35+	323.57±9.50+	307.24±8.57+
Series II				
Number of rats	17	15	10	11
Initial values	444.78±5.14	471.14±4.73	439.80±2.57	418.60±5.06
After administration of prazosin	472.82±4.12*	500.13±9.06*	472.04±9.67**	474.29±11.50**
propranolol	318.85±10.56+++	354.41±11.66+++	365.34±13.90+++	340.81±12.92+++

TABLE 3. Cardiac Output (ml/min) in Rat Pups after Consecutive Blockade of β- and α_1-Adrenoceptors

Experimental conditions	Age, days			
	21 (*n*=17)	30 (*n*=15)	42 (*n*=10)	70 (*n*=11)
Series I				
Initial values	28.32±0.98	35.45±1.99	51.80±2.91	75.91±8.90
After administration of propranolol	14.11±0.45**	19.20±1.74***	22.60±2.20***	44.53±3.52**
prazosin	7.67±0.80+++	11.79±1.58++	12.08±1.58+++	34.26±3.05+
Series II				
Initial values	21.84±1.98	42.41±3.00	53.77±4.19	75.80±7.43
After administration of prazosin	14.95±1.95*	30.69±4.09*	38.01±5.36*	45.00±7.54**
propranolol	6.95±0.96++	13.99±3.15++	18.84±2.11++	19.31±3.49++

old rats, the role of β- and α_1-AR in HR regulation is less significant. In 70-day-old rats, the response to propranolol 2.3 times surpassed that to prazosin. Our findings suggest that HR reaction to propranolol is more pronounced after preliminary blockade of α_1-AR. On the other hand, irrespective of the order of administration, HR reaction to prazosin is always lower than that to propranolol. Autoradiography revealed β_1- and β_2-AR in guinea pig sinus node [13]. It is known that prazosin completely prevents the positive chronotropic effect of norepinephrine [7]. The dose-dependent chronotropic effect of norepinephrine was observed in the presence of propranolol [7]. Therefore, both β- and α_1-AR participate in the regulation of HR.

The consecutive blockade of β- and α_1-AR with propranolol and prazosin showed that α_1-AR play a predominant role in the realization of sympathetic influences on SV in 21-day-old rats and that the role of β- and α_1-AR increases with age (30 and 42 days), but at the age of 70 days propranolol- and prazosin-induced changes in SV were less pronounced than at the age of 42 days.

These findings suggest that both β- and α_1-AR are involved in the regulation of SV in developing rats. The positive inotropic effect of α_1-AR agonists on the atria and ventricles of rat heart was reported by A. P. Williamson *et al.* [16].

Activation of β_1- and β_2-AR was shown to increase the total cAMP content in rat ventricles [17]. Therefore, blockade of these receptors prevented cAMP accumulation and reduced contractility of the myocardium. In the heart of adult rats, α_1-AR activation does not enhance Ca^{2+} current, but suppresses K^+ current. These effects can underlie the positive inotropic effect of α_1-adrenergic stimulation [17]. These data can also explain the decrease in SV after the blockade of α_1-AR observed in our study. Rat heart ventricles have both β_1- and β_2-AR, but their activation produces different effects. The accumulation of cAMP after activation of β_2-AR was half as much as after β_1-AR activation. The latter stimulated Ca^{2+} currents, and the amplitude of contractions varied in parallel with cAMP accumulation [17]. It is known that α_1B-AR are involved in the realization of positive inotropic effects of epinephrine on rat heart mediated by intracellular Ca^{2+} [12]. Sustained positive inotropic effects of α_1-agonists on the atria and ventricles of rat heart results from stimulation of α_1A- and α_1B-AR [16].

Our data indicate that adrenergic regulation of HR and SV are realized through α_1- and β-AR. This implies that α_1-AR play an important role in the regulation of not only inotropic, but also chronotropic function of the heart [14].

The density of α_1-AR in the sinoatrial and atrioventricular nodes is higher than in the myocardium [14].

When analyzing prazosin-induced changes in CO after its reaction to propranolol, we found that in 21-day-old rats, the sympathetic influences on CO are realized through β-AR rather than through α_1-AR. In 30-day-old animals, the sympathetic effects mediated by β- and α_1-AR were less pronounced, and 70-day-old rats showed the lowest sensitivity of CO to β- and α_1-AR blockade.

Therefore, from days 21 to 70 of life, both propranolol-induced blockade of β-AR and prazosin-induced blockade of α_1-AR against the background of a pronounced chronotropic reaction to propranolol reduced CO. These findings suggest the involvement of α_1- and β-AR in the regulation of CO in developing organism.

Series II revealed the increasing role of α_1-AR in sympathetic regulations. The contribution of β-AR to the sympathetic effects on CO was relatively high in 21-day-old rats, but decreased at the 42th day of life. The highest CO response to propranolol after the blockade of α_1-AR was observed in 70-day-old rats.

In conclusion, our findings indicate that both α_1- and β-AR participate in the realization of sympathetic influences on SV, HR, and CO in rats.

REFERENCES

1. R. A. Abzalov and R. R. Sitdikova, *Byull. Eksp. Biol. Med.*, **100,** No. 8, 172-174 (1985).
2. R. A. Abzalov and F. G. Sitdikov, *Developing Heart and Locomotor Activity* [in Russian], Kasan' (1998).
3. A. M. Badakva, *Changes in the Cardiac output of Circulation in Animals during Space Flight and in Model Experiments*, Abstract of Cand. Biol. Sci. Dissertation, Moscow (1989).
4. E. Sh. Minnibaev, *The Role of α_1- and β-Adrenoceptors in the Regulation of Cardiac Output in Developing Organisms*, Abstract of Cand. Biol. Sci. Dissertation, Kasan' (1996).
5. R. R. Nigmatullina, F. G. Sitdikov, and R. A. Abzalov, *Fiziol. Zh. SSSR*, No. 7, 965-969 (1988).
6. D. B. Bulyvd, D. C. Eikenberg, J. P. Hieble, *et al., Pharmacol. Rev.*, **46,** No. 2, 121- 136 (1994).
7. H. Kimura, S. Kawana, N. Kanaya, *et al,. Life Sci.*, **54,** No. 24, 451-456 (1994).
8. W. I. Kubicek, I. N. Karnegis, and R. P. Patterson, *Aerospace Med.*, **37,** No. 12, 1208-1212 (1966).
9. T. M. Laz, C. Forray, K. E. Smith, *et al., Mol. Pharmacol.* **46**, No. 3, 414-422 (1994).
10. A. Lazou, S. J. Fuller, M. A. Bogoyevitch, *et al., Am. J. Physiol.*, **267,** No. 3, Pt. 2, 970-978 (1994).
11. B. Le-Grand, A. Marty, B. Vie, *et al., Br. J. Pharmacol.*, **112,** No. 1, 195-199 (1994).
12. M. C. Michel, G. Hanft, and G. Gross, *Ibid.*, No. 2, 533-538.
13. F. D. Russell, A. R. Kompa, P. Mollenaar, and R. J. Summers, *Naunyn Schmiedeberg Arch. Pharmacol.*, **349,** No. 5, 463-472 (1994) .
14. K. Saito, T. Suetsugu, Y. Oku, *et al., Br. J. Pharmacol.*, **111,** No. 2, 465-468 (1994).
15. J. Salles, S. Gacson, D. Ivorra, and A. Badia, *Eur. J. Pharmacol.*, **266,** No. 1, 35-42 (1994).
16. A. P. Williamson, E. Seifen, J. P. Lindemann, and R. H. Kennedy, *J. Pharmacol. Exp. Ther.*, **268,** No. 3, 1174-1182 (1994).
17. R. P. Xiao, C. Hohl, R. Altschuld, *et al., J. Biol. Chem.*, **269,** No. 29, 19151-19156 (1994).