Blockade of Different Subtypes of α_1-Adrenoceptors Produces Opposite Effect on Heart Chronotropy in Newborn Rats

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 154, No. 8, pp. 144-146, August, 2012
Original article submitted February 2, 2011

We compared the effects of blockade of α_{1A}-, α_{1B}-, and α_{1D}-subtypes of α_1-adrenoceptors on the cardiac rhythm in newborn rats. Different responses of the heart were observed after blockade of several subtypes of α_1-adrenoceptors. Administration of WB 4101, a selective blocker of α_{1A}-adrenoceptors, increased heart rate, while blockade of α_{1AD}-adrenoceptors with BMY 7378 decelerated of heart rhythm. Blockade of α_{1B}-adrenoceptors with chloroethylclonidine produced no significant effects on heart chronotropy.

Key Words: *heart; α_1-adrenoceptor; sympathetic regulation; rat; ontogeny*

Sympathetic nervous system regulates the heart through activation of two types of adrenergic receptors (AR): α_1-AR and β-AR. In the heart, β_1-AR is most prevalent subtype, while β_2- and α_1-AR are less abundant, but play an important functional role. All AR activate G-proteins; β-AR activate mainly Gs -proteins; α_1-AR Gq-proteins, and β_2-AR Gi-proteins.

The role of β_2-AR in the regulation of heart rate, myocardial contractility, and pathological processes is well studied [1,3,11,12,15]. Cardiac α_1-AR are less studied. There are three subtypes of α_1-AR: α_{1A}, α_{1B}, and α_{1D} [9]. All three subtypes are activated by epinephrine and norepinephrine and blocked by prazosin [2]. All α_1-AR coupled with Gq-protein activate phospholipase Cb1 followed by diacylglycerol accumulation and protein kinase C activation. It is known that α_1-AR is present in the heart and is similar in different animal species, except rats [11]. In the heart, α_{1A} and α_{1B} AR are mainly located on the nuclear membrane of myocytes, but not on sarcolemma [14]. α_{1A}- and α_{1B}-Subtypes are most concentrated in the myocardium, whereas α_{1D}-subtype is predominant and functionally significant in the epicardial coronary arteries and smooth muscle cells [4-6,8,13]. *In vitro* and *in vivo* studies suggest that α_{1A}- and α_{1B}-subtypes in rat cardiomyocytes may have different regulation during chronic stimulation [10]. Thus, the questions about the role of different subtypes of α_1-AR in the regulation of the heart function are open and the contribution of α_1-AR subtypes into the regulation of heart rate in rat early postnatal ontogenesis is poorly understood.

Here we studied the effects of the blockade of various α_1-AR subtypes in newborn rats.

MATERIALS AND METHODS

The study was carried out on white outbred 7-day-old (newborn) rats (n=23). The animals were narcotized with 25% urethane (1000 mg/kg intraperitoneally). Selective blockers (Sigma), namely α_{1A}-AR blocker WB 4101 in a dose of 1 mg/kg, α_{1B}-AR blocker chloroethylclonidine in a dose of 5 mg/kg, and α_{1D}-AR blocker BMY 7378 in a dose of 1 mg/kg, were injected into the right femoral vein. ECG was visually monitored

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0007-4888/12/1542-0184

throughout the experiment; 21 parameters of ECG and variation pulsogram were recorded and processed.

Statistical analysis and the significance of differences were performed by Student's *t* test using Microsoft Excel software.

RESULTS

Introduction of α_{1A}-AR selective blocker WB 4101 to 7-day-old rats reduced the mean cardiointerval (Xm). Xm changed from 135.00±2.70 to 131.70±3.14 msec 1 min after injection and then continued to decrease to 126.5±2.9 msec 5 min after injection, 122.8±3.8 msec 15 min after injection ($p<0.05$), and 121.0±4.2 msec at the end of observation ($p<0.05$; Fig. 1).

Analysis of heart rate variability revealed a very interesting fact: significant decrease in mode amplitude (AMo) after injection. This indicator best reflects sympathetic activity of the autonomic nervous system. However, we observed no decrease in heart rate; on the contrary, a slight decrease in Xm was recorded.

Intravenous administration of selective α_{1B}-AR blocker chloroethylclonidine did not change significantly Xm in 7-day-old rats. Xm was increased from 131.0±3.7 to 138.0±4.1 msec after 1 min and to 139.0±3.6 msec after 5 min (Fig. 1). Then, Xm value changed insignificantly.

The selective blockade of α_{1D}-AR with BMY 7378 decelerated heart rate in 7-day-old rats. Interestingly, Xm value remained virtually unchanged: 156.5±4.7 *vs.* 155.2±4.1 msec (initial value), but then bradycardia became more pronounced: Xm increased to 164.5±5.8 msec in 5 min after injection of BMY 7378 and the increase in Xm became significant in 15 min reaching 174.7±6.6 msec. Then, the heart rate progressively decreased, and duration of Xm was 180.7±7.9 msec after 30 min ($p<0.05$; Fig. 1).

Thus, we revealed specific features of cardiovascular regulation by different α_1-AR subtypes in newborn rats. Selective blockade of α_{1A}-AR with WB 4101 increased heart rate. On the contrary, blockade of α_{1D}-AR led to deceleration of heart function, while antagonist of α_{1B}-AR did not change significantly heart rate. The results suggest that both β-AR and α_1-AR contribute to adrenergic regulation of the neonatal rat heart. It is possible that different α_1-AR subtypes have opposite functions in the absence of sympathetic innervation of the heart. It may be that in newborn rats, α_{1A}-AR regulates the heart not via Gi protein, but via Gq protein; the expression of these protein is age-dependent. At the same time, significant response of the heart rhythm to α_{1D}-AR blockade is worthy of note, although their functional role in the heart is controversial [4,5,13].

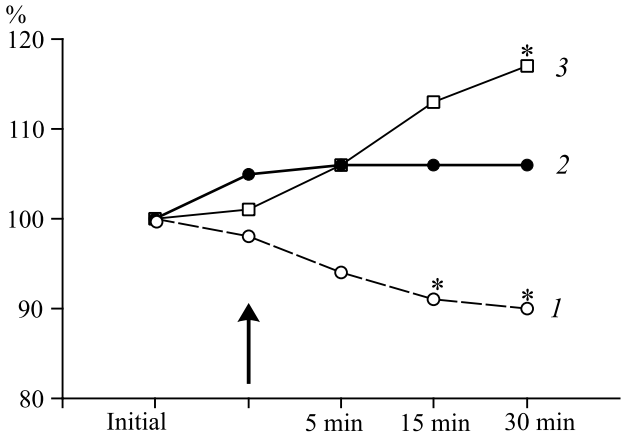

Fig. 1. Dynamics of Xm under conditions of selective blockade of α_{1A} (*1*), α_{1B} (*2*), and α_{1D} (*3*) subtypes of α_1-AR in newborn rats. Arrow shows time of blocker administration. *$p<0.05$ in comparison with initial values.

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