PHYSIOLOGY

Age-Related Peculiarities of Adrenergic Regulation of Cardiac Chronotropic Action after I_f Blockage

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The effects of norepinephrine on the heart rate were studied in 1-, 3-, 6-, and 20-week-old rats before and after blockade of hyperpolarization-activated currents (I_f, I_h). In animals with mature sympathetic regulation of cardiac activity (6- and 20-week-old animals), I_f blockage decreased the severity of norepinephrine-induced tachycardia. In newborn rats lacking sympathetic innervation of the heart, norepinephrine only slightly affected heart rate before and after I_f blockage. In 3-week-old animals, I_f blockage after norepinephrine pretreatment increased tachycardia.

Key Words: *heart; hyperpolarization-activated currents; chronotropic action; ontogeny*

The sinoatrial node in mammals is innervated by autonomic nerves regulating cardiac chronotropy. According to classical concept, activation of the sympathetic part of the autonomic nervous system (ANS) leads to acceleration and activation of the parasympathetic part induces deceleration of the heart rate (HR). Epinephrine and acetylcholine modulate HR by regulating ion currents playing a key role in pacemaker activity of atypical myocardiocytes of the sinoatrial node (I_f, "funny" currents) [6]. Activated during hyperpolarization non-selective cation currents are also found in intracardiac neurons [10]. The mechanisms of modulation of these currents under normal and pathological conditions are intensively studied [3,12,15]. I_f have been found in not only conducting system cardiomyocytes and in working cardiomyocytes [5]. Our previous experiments revealed significant age-related features of chronotropic and inotropic response of rat heart to I_f blockage [1,2]. It has been demonstrated that I_f blockage in pigs and rabbits attenuated HR acceleration induced by adrenoreceptor agonists, but does not affect the increase in heart contraction force [9,13]. I_f activity has been found to depend on intracellular level of cAMP, the main transmitter of catecholamine effects on the heart [7]. Activity of the sympathetic part of human ANS slowly increases with age [4,14]. At the same time, coupling of β-adrenoreceptors with Gs-protein and adenylate cyclase is impaired with age [8,11].

Here we studied age-related features of I_f influence on the effects of non-selective adrenoreceptor agonist norepinephrine (NE).

MATERIALS AND METHODS

The experiments were performed on 1-, 3-, 6-, and 20-week-old rats (n=65). Adrenergic heart regulation is absent in newborn rats and develops starting from the third week of life. The age of 6 weeks corresponds to prepuberal stage and 20-week-old rats are suggested to be mature.

The rats were narcotized with 1000 mg/kg urethane (25% solution, intraperitoneally).

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For evaluation of the role of I_f in the realization of regulatory effects on rat heart at various terms of postnatal ontogeny, 2 series of experiments were performed in each age group: NE was injected to intact animals (series I) or against the background of I_f blockage (series II).

I_f blocker ZD-7288 (Tokris) in a dose of 0.07 mg/kg and non-selective adrenoreceptor agonist NE (Sigma) in a dose of 0.01 mg/kg were injected into the right femoral vein. ECG recording and computer processing of ECG and variation pulsogram were performed throughout the experiment.

The data were processed and significance of between-group differences was evaluated using the Student and Wilcoxon tests.

RESULTS

Intravenous administration of NE increased HR (Fig. 1). The duration of average RR interval (X_{av}) decreased from 196.00±8.83 to 167.00±5.85 msec ($p \leq 0.05$) by minute 1 after substance injection; in 5 and 30 min after injection, X_{av} was 181.00±8.97 and 190.00±7.42, respectively. Administration of I_f blocker ZD-7288 to 20-week-old rats was followed by a smooth decrease in HR from 186.00±16.39 to 242.0±15.15 msec ($p \leq 0.05$, Fig. 2). NE administered against the background of ZD-7288 treatment decreased X_{av} from 242.00±15.15 to 219.00±13.89 (*i.e.* by 10% in mature rats, $p \leq 0.01$; Fig. 2); 1 minute after treatment this parameter was 227.00±14.99 msec (*i.e*. 7% from the initial level); 10 min after injections X_{av} returned to the baseline (242.00±10.04 msec).

NE administration to 6-week-old rats reduced X_{av} from 143.00±4.71 to 124.00±2.34 msec ($p \leq 0.05$); this parameter was 127.00±3.15 msec after 1 min ($p \leq 0.01$) and returned to the initial level in 15 min after injection (Fig. 1). I_f blocker increased X_{av} in these rats from 132.00±2.60 to 182.00±10.23 msec ($p \leq 0.05$; Fig. 3). NE injection against the background of ZD-7288 treatment induced a transient increase in HR. During minute 1, X_{av} decreased from 182.00±10.23 to 166.00±9.49 msec (by 9% from the initial level, $p \leq 0.05$; Fig. 3), while by minute 7, HR returned to 182.00±10.21 msec.

Intravenous injection of NE to 3-week-old rats did not significantly change HR: X_{av} decreased from 123.00±3.05 to 118.00±3.39 msec by minute 3 after NE administration and was 124.00±6.10 msec on minute 15 (Fig. 1). Blockade of hyperpolarization-activated currents in 3-week-old rats was followed by an increase in X_{av} from 120.00±1.96 to 152.00±4.98 msec ($p \leq 0.01$, Fig. 2). NE administration after I_f blockage in 3-week-old animals resulted in a decrease in X_{av} from 152.00±4.98 to 137.00±4.03 msec ($p \leq 0.05$, Fig. 2). By

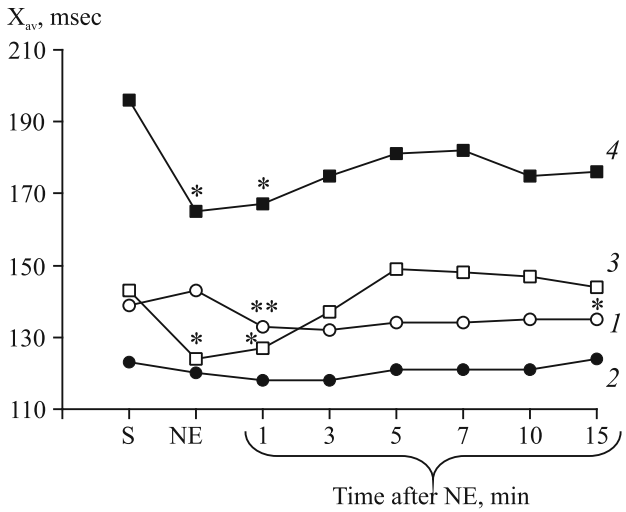

Fig. 1. Age-related features of HR response to NE administration. *1*) 1-week-old; *2*) 3-week-old; *3*) 6-week-old; *4*) 20-week-old animals. Here and in Figs. 2 and 3: S: stabilization; NE: NE administration. *$p \leq 0.05$ and **$p \leq 0.01$ in comparison with the initial level (stabilization).

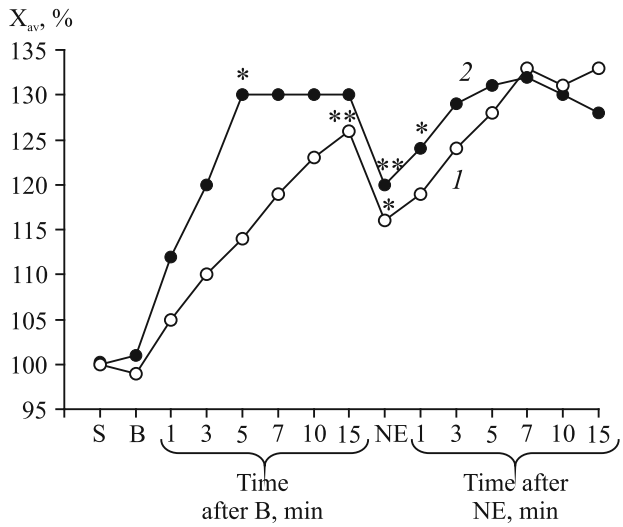

Fig. 2. Dynamics of X_{av} after NE administration and I_f blockage in 3-week-old (*1*) and 20-week-old (*2*) rats. Here and in Fig. 3: B: administration of I_f blocker ZD-7288.

minute 3, X_{av} was 150.00±4.12 msec and by minute 15, this parameter was 163.00±6.83 msec.

NE administration to 1-week-old rats was followed by a decrease in X_{av} from 134.00±0.71 to 127.00±0.48 msec in 1 min after injection ($p \leq 0.01$). By minute 15, X_{av} was 131.00±0.64 msec ($p \leq 0.05$, Fig. 1). Administration of I_f blocker increased X_{av} in newborn animals from 136.00±1.61 to 173.00±9.18 msec ($p \leq 0.05$, Fig. 3). NE injected to newborn rats after I_f blockage slightly reduced X_{av} from 173.00±9.18 to 164.00±8.19 msec (by 5%, $p \leq 0.05$; Fig. 3). On minute 5 of the experiment, X_{av} was 169.00±9.02 msec.

Thus, significant age-related features of rat heart response to NE administration were observed before

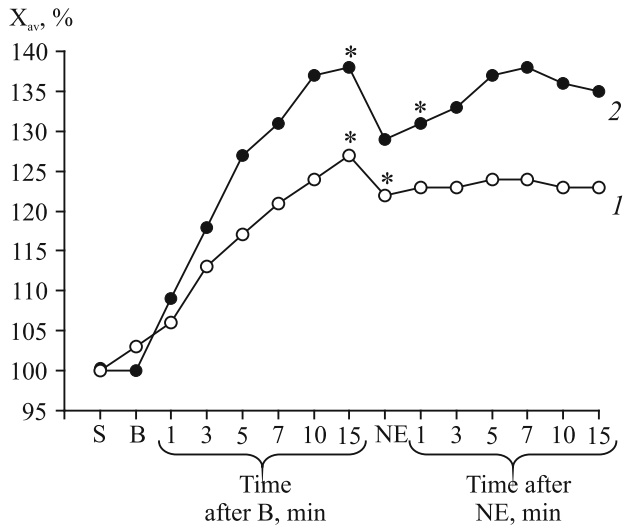

Fig. 3. Dynamics of X_{av} after NE administration and I_f blockage in 1-week-old (*1*) and 6-week-old (*2*) rats.

and after the blockage of hyperpolarization-activated currents. Preliminary I_f blockage did not prevent the increase in the HR after NE injection in all age groups. Our findings suggest that NE-induced increase in HR was less pronounced in animals with formed sympathetic heart regulation (in 20-week-old rats: 15% before I_f blockage ($p \leq 0.05$) and 10% after I_f blockage ($p \leq 0.05$); in 6-week-old animals, 13% before I_f blockage ($p \leq 0.05$) and 9% after I_f blockage). In newborn rats without sympathetic heart innervations, NE increased HR by 5% both before and after I_f blockage ($p \leq 0.05$). Administration of I_f blocker to 3-week-old animals potentiated the effect of NE. NE increased HR by 4% before I_f blockage and by 10% after I_f blockage ($p \leq 0.05$). We have previously demonstrated some peculiarities of chronotropic and inotropic response of the heart to I_f blockage in 3-week-old rats [1,2]. It can be hypothesized that age-related changes in functional activity of the sympathetic part of ANS [4] affect the interactions between ANS and I_f. These data should be taken into account during correction of tachyarrhythmias with I_f blockers.

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