DOI 10.1007/s10517-015-2947-0

Role of 5-HT$_{2B}$ Serotonin Receptor Agonist in the Regulation of Pumping Function of the Heart

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 159, No. 3, pp. 278-280, March, 2015
Original article submitted October 8, 2014

The effect of α-methyl-5-hydroxytryptamine maleate, an agonist of 5-HT$_{2B}$ serotonin receptors, on the pumping function of the heart was examined in rats with forced motor behavior. At rest, swim-trained rats demonstrated lower HR and greater stroke volume and cardiac output than untrained rats. The agonist decreased HR, stroke volume, and cardiac output in 21- and 70-day-old swim-trained rats, but not in 100- and 200-day-old rats.

Key Words: *muscle training; heart rate; stroke volume; cardiac output; 5-HT$_{2B}$ serotonin receptor agonist*

During postnatal ontogeny, serotonin exerts both stimulating and inhibitory age-dependent effects on the pumping function of rat heart and mechanisms of its regulation [1,4,6,7]. The responses of cardiac serotonin receptors were examined on 70-day-old rats subjected to muscle training [6]. To study the mechanisms of pumping function regulation, the regimens of swimming training were elaborated for rats at the Department of Physical Exercise Physiology, Kazan Federal University [5,8,10].

Here we studied the role of 5-HT$_{2B}$ serotonin receptors in the regulation of pumping function of the heart during the growth and development of the rats with forced motor activity.

MATERIALS AND METHODS

Experiments were carried out on the rats aging 21, 70, 100, and 200 days. In each age group, the experimental rats were subjected to forced motor activity in contrast to the control animals with unrestricted motor behavior.

The experimental rats were adapted to swimming with stepwise increasing load. On training day 1, the duration of exercise was 5 min and then the duration of single training session increased by 5 min in every other day, so to the end of training week 2, it maximized to 30 min. The total training duration increased every day by 10 min, so to the end of training week 4, it attained 90 min. During training week 5, the experimental rats were subjected to swimming for 90 min, including a 30-min loaded forced swimming test with a 3% body weight load. During the loaded forced swimming test, a metal load was fixed to the body with a fine rubber band in such a way that it did not impede respiration. The same regimen was employed on training week 6 except for increasing the load to 5% body weight. During training weeks 7 to 26, the duration of swimming test with a 5% body weight load was 60 min. The experimental rats were subjected to swimming training sessions for 6 days in a week.

The control rats were maintained under the conditions of free motor behavior. They were kept by 5-6 animals per cage and demonstrated spontaneous motor behavior that was neither restricted, nor stimulated.

To study HR, stroke volume (SV), and cardiac output (CO), the rats were narcotized with urethane (800 mg/kg body weight) and the differential and integral rheograms were recorded under natural respiration [9] using a modified method [3].

In 10-15 min after injection of urethane, α-methyl-5-hydroxytryptamine maleate (Tocris), an agonist of 5-HT$_{2B}$ serotonin receptors, was injected three times

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into the femoral vein via a catheter in increasing doses of 1, 10, and 30 mg/kg, the interval between injections was 10 min [11]; the maximum changes in HR, SV, and CO were recorded after each dose.

The data were analyzed statistically using Chart, Claris Works, and Statistica 6.0 softwares. Significance was assessed by Student's *t* test at $p \leq 0.05$.

RESULTS

At rest, HR in 70-day-old swim-trained animals was lower by 118.1 bpm than that in 21-day-old ones ($p \leq 0.05$) and by 9 bpm higher than in 70-day-old controls. Further decrease of HR at rest was observed in 100-day-old rats in comparison with 70-day-old animals. The difference in HR of control and experimental rats was used as the indicator of efficacy of muscle training. In 70-day-old rats, this difference was 28.8 bpm ($p \leq 0.05$). In 200-day-old experimental rats, HR at rest (290.0±4.1 bpm) was lower by 19.2 bpm than that in age-matched controls ($p \leq 0.05$).

In 21-day-old rats, SV at rest was 0.074 ml. In 70-day-old experimental animals, it increased to 0.225 ml ($p \leq 0.05$). At this age, SV in control rats was lower by 0.031 ml than that in the age-matched experimental animals ($p \leq 0.05$). In 100-day-old experimental rats, SV was higher by 0.039 ml than in control animals. In 200-day-old experimental rats, SV was 0.362±0.006 ml and surpassed the control value by 0.032 ml ($p \leq 0.05$). Thus, SV increased with age in all rats, but the increments were more pronounced in experimental (swim-trained) rats.

In 21-day-old rats at rest, CO was 36.16±1.80 ml/min. In 70-day-old experimental animals, it increased by 73.49 ($p \leq 0.05$). In 100-day-old experimental rats, CO somewhat decreased, which evidently reflected the drop in HR at rest. In 100- and 200-day-old experimental rats, CO was similar.

In 21-day-old rats, the first dose of the agonist decreased HR by 26 bpm on postinjection minute 10 ($p \leq 0.05$). The second dose of this agent induced further drop in HR by 22 bpm on postinjection minute 10, so the total drop was 48 bpm ($p \leq 0.05$). Thus, two injected doses of the agonist pronouncedly decreased HR in 21-day-old rats.

In 70-day-old experimental rats, the first dose of the agonist decreased HR by 37.2 bpm on postinjection minute 10 ($p \leq 0.05$). In comparison with the second dose, the third one produced no significant changes in HR. In 100-day-old experimental rats, the first dose of the agonist produced somewhat lower decrement in HR than that in 70-day-old rats. In 100-day-old control rats, the agonist decreased HR by 13.1 bpm ($p \leq 0.05$). In 200-day-old rats, all doses of the agonist produced no significant changes in HR. Thus, the most pronounced changes in HR induced by the agonist of 5-HT_{2B} serotonin receptors were observed in 21-day-old rats, while in 70-day-old rats the corresponding HR changes were slightly lower. In contrast, the agonist produced no significant changes in HR of 100- and 200-day-old rats.

In 21-day-old control rats, the first dose of the agonist decreased SV. After the second dose, the decrement was more pronounced (in comparison with initial values), being 0.032 ml ($p \leq 0.05$). In 70-day-old experimental rats, the second dose of agonist decreased SV by 0.029 ml on postinjection minute 10 ($p \leq 0.05$). In 70-day-old control rats, the third dose of agonist decreased SV by 0.027 ml ($p \leq 0.05$). No changes in SV were observed in 100- and 200-day-old rats after three injections of the agonist.

In 21-day-old control rats, the first dose of the agonist decreased CO to postinjection minute 6 ($p \leq 0.05$). A more pronounced drop of CO (by 19.75 ml/min, $p \leq 0.05$) was observed after the third injection. In 70-day-old experimental rats, the second dose of the agonist decreased CO by 22.15 ml/min ($p \leq 0.05$). In age-matched control rats, CO dropped by 18.1 ml/min ($p \leq 0.05$). In 100-day-old experimental rats, the third dose of the agonist decreased CO by 11.4 ml/min ($p \leq 0.05$). In age-matched control rats, the third dose of the agonist insignificantly decreased CO by 6.7 ml/min ($p > 0.05$). In 200-day-old control and experimental rats, the agonist-induced drop in CO was no more than 3 ml/min ($p > 0.05$). Thus, only 21- and 70-day-old rats demonstrated significant CO decrement after injection of the agonist of 5-HT_{2B} serotonin receptors.

The observed effects of forced motor activity on HR, SV, and CO refined the peculiarities of cardiac pumping function modulation during regular muscle training [1,2,6]. Therefore, α-methyl-5-hydroxytryptamine maleate, an agonist of 5-HT_{2B} serotonin receptors, decreased the indices of cardiac pumping function. The most pronounced drops in HR, SV, and CO were observed in 21-day-old rats. In 70-day-old rats, the decrements of these parameters were less pronounced, but still significant. However, in 100- and 200-day-old rats, the examined serotonin agonist did not significantly change HR, SV, and CO. Thus, α-methyl-5-hydroxytryptamine maleate, an agonist of 5-HT_{2B} serotonin receptors, reduced the indices of cardiac pumping function only at the early stages of ontogeny (in 21- and 71-day-old rats).

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