

# Influence of 5-HT<sub>2</sub> Receptor Agonist on Cardiac Pumping Function of Trained Offspring of Trained Rats

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We studied cardiac pumping function in the offspring of rats subjected to swimming exercise and the offspring of untrained rats. The rat pups were adapted for swimming with stepwise increasing load from day 21 to 70 life. At the age of 21 and 70 days, offspring of trained rats showed lower HR and significantly higher stroke volume and cardiac output than offspring of untrained rats. Agonist of 5-HT<sub>2</sub>-receptors  $\alpha$ -methyl-5-hydroxytryptamine maleate (30  $\mu$ g/kg) reduced enhanced stroke volume in trained offspring born by trained mothers. In trained offspring of untrained rats, the agonist had more pronounced effect on HR.

**Key Words:** *muscle exercise; cardiac pumping function; heart rate; stroke volume; 5-HT<sub>2</sub> receptor agonist*

Questions whether properties of trained heart may be inherited by subsequent generation are still open. Studies of juvenile sportsmen who were born from the sportswomen has not yet shed light on this problem, because it seems to be quite difficult to maintain fitness level throughout the human life. Animal experiments seem to be promising in this respect. Attempts have been made to study cardiac pumping function in offspring of trained female rats [1-3]. However, these few works did not clarify the problem. Further research is obviously required to study whether it is possible to transfer characteristics of cardiac pumping function of trained heart from parents to offspring.

In recent years, more attention has been paid to the role of serotonin (5-HT) in the regulation of the cardiovascular system. It is shown that 5-HT produces a positive inotropic effect on atrial and ventricular myocardium in several mammalian species including guinea pig, monkey, cat, pig, rabbit, and man. However, the data on the effect of 5-HT on inotropic myocardial function in rats are contradictory [8]. Little is

known on age-related characteristics of 5-HT-regulation of myocardial contractility in most mammals including rats. In the developing heart, 5-HT via 5-HT<sub>2B</sub> receptors regulates differentiation and proliferation of cardiomyocytes [11] and enhances myocardial contractility [5]. Increased stroke volume (SV) is accompanied by the development of cardiac hypertrophy. 5-HT via 5-HT<sub>2</sub> receptors along with epinephrine contributes to this process [7,9,12].

The aim of the work was to study the characteristics of cardiac pumping function of trained heart in the offspring of trained females under the action of the drug  $\alpha$ -methyl-5-hydroxytryptamine maleate (Tocris).

Here we studied the characteristics of cardiac pumping function of trained heart manifested in the subsequent generation of rats as well as the impact of 5-HT<sub>2</sub> receptor agonist on the cardiac pumping function in the trained offspring of trained and untrained mothers [4].

## MATERIALS AND METHODS

The experiments were carried out on 21- and 70-day-old white laboratory rats. Pregnant females and then their offspring were subjected to stepwise increa-

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sing swimming load. The pups were divided into two groups: offspring of trained (group 1) and untrained mothers (group 2). The pups of both groups were kept under standard vivarium conditions (6-8 animals per cage) and fed similar diet.

The whole cycle of swimming training consisted of preparatory, basic, and final stages. During the 2-week preparatory stage, the pups were forced to swim in a bath at 32-33°C and swimming duration increased from 5 min on day 1 to 30 min on day 14 (*i.e.* by 5 min every other day). At the preparatory stage, the animals were habituated to regular exercise.

The basic stage of training lasted from the 3rd to 4th week. By the end of the second week, the pups were well adapted to swimming. They were easily floated near the bath walls by slightly moving their front legs. At the basic stage of training, water current in the bath was modeled. The length of each training session increased by 10 min and was 90 min up to the end of the basic stage. The aim of the basic stage was to develop adapting skills and increase training intensity.

The aim of the final 21-day stage of swimming training (starting from the 5th week) was to intensify exercise. Therefore, starting from the 5th week of training the pups swam with a load equal to 3% of body weight for one week (90 min swimming including 30 min with the load). The load was fixed with a thin elastic band so that it did not interfere with breathing. During the 6th week, the pups swam with a load of 5% body weight (90 min swimming including 30 min with the load). During the 7th week, the time of swimming with a load corresponding to 5% of body weight was 60 min. Thus, the intensity of exercise at the final stage was increased by using metal loads at a constant training time. The animals were trained 6 days a week. After each training session, the animals were wiped with a dry cloth and dried in special cages under the lamp for preventing the disease. The previously developed training regimen for growing rats was used [2].

Rheography is widely used among the various methods of determining SV. Tetrapolar impedance plethysmography that is used for assessing cardiac output is a variant of this technique [10]. The method is based on recording of electrical resistance of living tissues which varies during blood supply fluctuations during the cardiac cycle at the moment of passage of high frequency low voltage current through these tissues [6]. Tetrapolar impedance plethysmography is characterized by high accuracy and reproducibility of measurements; it is easy to use, painless, and harmless.

Volume and differentiated rheogram were recorded in rats narcotized with chloral hydrate (40 mg/kg body weight) during spontaneous respiration by means of an RPG-204 rheoplethysmograph. Needle electrodes were

introduced under the skin: the first and fourth current electrodes were fixed on the head and the foot and the second and third potential electrodes were positioned parallel to each other over the middle of the clavicle and xiphisternum.

$\alpha$ -Methyl-5-hydroxytryptamine maleate was injected into the femoral vein through a catheter 10-15 min after injection of anesthesia. Indicators of cardiac pumping function were recorded 2, 4, 6, 8, and 10 min after drug administration.

SV was calculated by the formula [10]:

$$SV = L^2/R^2 \times Ad \times tu \times p,$$

where SV is stroke volume (cm<sup>3</sup>),  $p$  is specific resistance of the blood ( $\Omega \times \text{cm}$ ),  $L$  is the distance between the measuring electrodes (cm),  $R$  is impedance between the electrodes ( $\Omega$ ),  $Ad$  is the amplitude of differentiated rheogram ( $\Omega \times \text{sec}$ ), and  $tu$  is ejection time (sec).

For calculation of the amplitude and time of blood ejection, the values from 10 cycles were averaged. Cardiac output (CO) was calculated as the product of SV and HR.

The results were analyzed using Chart, Claris Works and Igor Pro software in Macintosh operating system; Statistica 6.0 SR soft in Windows XP operating system. The data were statistically processed using common methods of variation statistics. Significance of differences was determined by Student's  $t$  test.

## RESULTS

In 21-day-old pups of group 2, HR was higher by 14.98 bpm ( $p < 0.05$ ) than in group 1 rats. SV in group 1 was higher by 35% ( $p < 0.05$ , Table 1). CO is an integral parameter that depends on HR and SV. At the age of 21 day, CO in group 1 was higher by 31.2% than in group 2 ( $p < 0.05$ ). Hence, 21-day-old offspring of trained females showed lower HR and significantly higher SV and CO than the offspring of untrained mothers. This is characteristic of the body with well-trained muscles [3].

At the age of 70 days, HR in young rats of group 2 was higher by 25 bpm than in group 1 ( $p < 0.05$ ). SV in group 1 was higher by 13% than in group 2 ( $p < 0.05$ ) and CO in trained rats of group 1 was also higher by 5.7% ( $p < 0.05$ , Table 1). Hence, the features of trained heart are more pronounced in 70-day-old offspring of trained mothers.

Injection of 5-HT<sub>2</sub> receptor agonist  $\alpha$ -methyl-5-hydroxytryptamine maleate reduced SV, HR, and CO (Table 2).

However, the severity of the negative impact of 5-HT<sub>2</sub> receptor agonist on HR and SV varied (Fig. 1).

**TABLE 1.** Parameters of Cardiac Pumping Function in Offspring of Trained and Untrained Mothers ( $M \pm m$ )

Age, days	Group 1 (trained mothers)			Group 2 (untrained mothers)		
	HR	SV	CO	HR	SV	CO
21	482.59±4.49	0.054±0.008	26.12±0.28	497.57±7.12*	0.040±0.004*	19.90±0.12*
70	345.43±6.48	0.368±0.005	127.11±1.90	370.11±6.21*	0.325±0.021*	120.28±2.92*

**Note.** \* $p < 0.05$  in comparison with group 1.

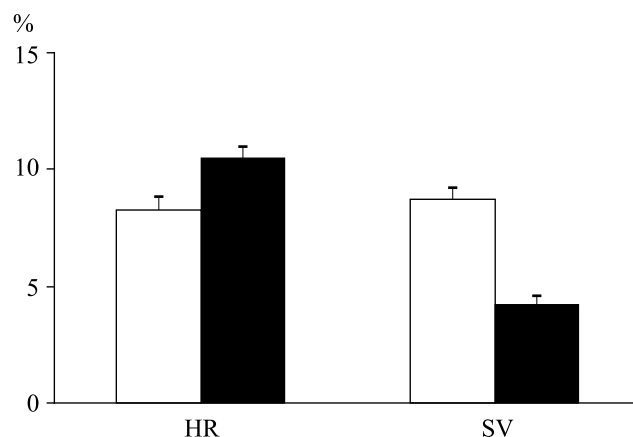
**TABLE 2.** Influence of 5-HT<sub>2</sub> Receptor Agonist on Cardiac Pumping Function of 70-Day-Old Offspring of Trained and Untrained Mothers ( $M \pm m$ )

Conditions after administration of 5-HT <sub>2</sub> receptor agonist	Group 1 (trained mothers)			Group 2 (untrained mothers)		
	HR	SV	CO	HR	SV	CO
Baseline	335.57±9.16	0.345±0.015	115.77±2.87	364.43±8.32*	0.313±0.015	114.06±2.43
2 min	316.60±5.47	0.319±0.022	101.02±5.57	335.15±3.87*	0.307±0.023	102.89±3.37
4 min	313.00±5.44	0.315±0.021	98.62±5.04	334.78±4.76*	0.306±0.019*	102.44±6.14
6 min	309.60±5.09	0.326±0.239	100.93±5.67	331.67±5.19	0.304±0.039	100.82±5.17
8 min	307.6±6.74	0.319±0.205	98.13±5.18	326.34±4.09*	0.300±0.025	97.90±4.18
10 min	310.9±4.93	0.318±0.023	98.87±5.92	326.40±4.43*	0.301±0.030	98.24±6.95

**Note.** \* $p < 0.05$  in comparison with group 1.

Trained pups in group 2 showed the maximum decrease in HR: by 38.09 bpm or 10.45% ( $p < 0.05$ ). However, trained young rats in group 1 demonstrated maximum decrease in SV: by 0.03 ml or 8.7%. Therefore, we hypothesized that 5-HT<sub>2</sub> receptor agonist reduces HR and SV in trained 70-day-old rats, but the magnitude of maximal response varies. The agonist reduced the enhanced SV in group 1, while in group 2 it affected HR to a greater extent. Identified negative inotropic and chronotropic effects of 5-HT<sub>2</sub> receptor agonist can be related to the protection of the heart from 5-HT excessively produced during exercise [6]. A possible mechanism can be Gi-protein activation, which leads to inhibition of myocardial function via intracellular transmitters.

Thus, parameters of the cardiac pumping function (HR, SV, and CO) in 21-day-old offspring of trained mothers differed significantly from those of coeval offspring of untrained mothers. This suggests that the characteristics of cardiac pumping function of trained heart are transmitted to the offspring. This difference persists for 70 days of life during muscle exercise. Agonist of 5-HT<sub>2</sub>-receptors reduced elevated SV in trained offspring from trained females and affected HR to a greater extent in the offspring of untrained



**Fig. 1.** Maximum response of SV and HR to administration of 5-HT<sub>2</sub> receptor agonist to trained offspring of trained (group 1) and untrained (group 2) mothers.

mothers.

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