DELTA SLEEP-INDUCING PEPTIDE MODULATES THE ACTION OF MEDIATORS ON THE HEART

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UDC 615.361.81:547.96].015.4.612.178.1].2].076.9

Key Words: delta sleep-inducing peptide; acetylcholine; noradrenalin; heart.

Delta sleep-inducing peptide (DSIP) increases the resistance of cardiovascular functions to emotional stress [5, 7]. This is due both to the central antistressor action of DSIP [2, 7] and to its direct effect on the heart and on extracardiac regulation [3, 4, 8]. The writers showed previously that DSIP strengthens parasympathetic and weakens sympathetic influences on cardiac activity [4, 8]. One of the mechanisms of these changes may be interaction between DSIP and mediators at the peripheral synapse level.

In this investigation interaction between DSIP and noradrenalin on the cardiac rhythm was studied on isolated rabbit hearts.

EXPERIMENTAL METHOD

Experiments were carried out on 51 isolated chinchilla rabbit hearts. The hearts were perfused through the coronary arteries by Langendorff's method with Tyrode solution (in mM): NaCl – 137.0, KCL – 2.7, $CaCl_2$ – 1.8, $MgCl_2$ – 1.0, $NaHCO_3$ – 12.0, NaH_2PO_4 – 0.4, glucose – 5.5. The solution was saturated with carbogen (95% O_2 and 5% CO_2) and pumped into the heart under constant pressure of 80 mm Hg. The temperature of the solution was 36 ± 0.3°C and pH 7.3-7.4. Monophasic action potentials were recorded by means of bipolar silver suction of electrodes, applied to the atrium and left ventricle, and led through a UBP 4-03 amplifier to an N338-4P recorder. In eight control experiments the time course of the spontaneous change in the rate of contraction of the isolated hearts was observed during perfusion for 40-45 min with Tyrode solution. The action of DSIP on the intact isolated rabbit heart and interaction of the peptide with acetylcholine or noradrenalin on the rate of contraction of the isolated heart were studied in 43 experiments. Immediately before the experiment the test substances were dissolved in Tyrode solution: DSIP in a concentration of $6 \cdot 10^{-6}$ M, acetylcholine 10^{-6} M, and noradrenalin 10^{-6} M. The duration of each experiment did not exceed 40-45 min.

EXPERIMENTAL RESULTS

In eight control experiments, when changes in the rate of contraction of the isolated hearts were investigated during perfusion with Tyrode solution for 40-45 min, the rate showed a slight tendency to fall. For instance, the heart rate (HR) changed from 91.4 ± 5.6 to 84.1 ± 4.6 beats/min ($p > 0.1$), evidence of a quite stable level of heart beat during this period of perfusion.

The action of DSIP on intact isolated rabbit hearts was studied in eight experiments. The initial HR in these experiments was 92.1 ± 5.4 beats/min. Perfusion with Tyrode solution containing DSIP ($6 \cdot 10^{-6}$ M) for 40-45 min did not lead to any significant changes in HR compared with the control experiments. Thus DSIP has virtually no effect on HR.

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Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 109, No. 5, pp. 419-420, May, 1990. Original article submitted May 26, 1989.

0007-4888/90/0005-0549$12.50

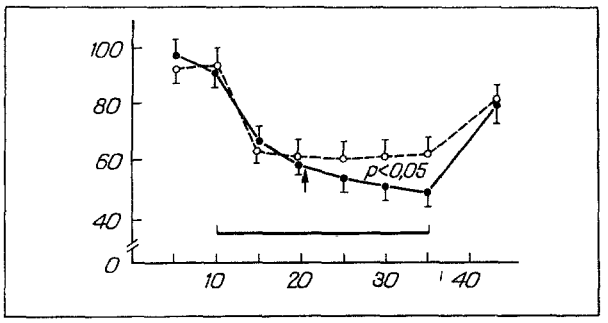

Fig. 1. Strengthening of negative chronotropic effect of acetylcholine on isolated rabbit heart under the influence of DSIP. Broken line shows time course of change in HR of hearts perfused with Tyrode solution with acetylcholine; continuous line — the same, for hearts perfused with Tyrode solution with acetylcholine and DSIP; arrow indicates time of addition of peptide to perfusion solution. Straight line indicates duration of perfusion with Tyrode solution containing acetylcholine. Here and in Fig. 2: abscissa, time (in min); ordinate, HR (beats/min).

Interaction of DSIP with acetylcholine on HR was studied in 16 isolated rabbit hearts. Changes in the response of HR to acetylcholine during combined perfusion with a solution of the mediator (10^{-6} M) containing DSIP ($6 \cdot 10^{-6}$ M). The initial HR was 92.8 ± 6.3 beats/min. The hearts were perfused for 10 min with Tyrode solution containing acetylcholine to determine the initial value of the negative chronotropic effect, which was 36.3% (HR fell to 59.1 ± 4.4 beats/min; $p < 0.05$), and it remained virtually unchanged throughout the period of perfusion with this solution.

Experiments were then carried out by two schemes: I) immediately after the testing response five hearts were perfused with the same Tyrode solution containing acetylcholine, but with the addition of DSIP. In this case the peptide strengthened the negative chronotropic effect of acetylcholine and reduced HR to 49.0 ± 5.3 beats/min (by 47.2%; $p < 0.02$; Fig. 1); II) five hearts after a 10-min testing response to acetylcholine were reperfused with Tyrode solution until recovery of HR. Perfusion with the same Tyrode solution with acetylcholine, but with addition of DSIP, was again carried out 10 min after restoration of the heart rate to 83.4 ± 7.7 beats/min. In this case the presence of DSIP in the perfusion solution also led to strengthening of the negative chronotropic effect of acetylcholine (to 49.7 ± 5.0 beats/min; $p < 0.05$) compared with the test response.

Control experiments were carried out on six isolated hearts. Scheme I was used for three experiments in which the hearts were perfused with acetylcholine solution for 30 min; scheme II was used for the other three, when the hearts were reperfused with Tyrode solution after the testing response to the mediator, after which perfusion with acetylcholine solution was repeated. Strengthening of the effect of acetylcholine compared with the testing response was not observed in any of the control experiments. Hence it can be concluded that DSIP has a potentiating effect on the negative chronotropic effect of acetylcholine on the isolated heart.

Interaction of DSIP with noradrenalin on HR was studied in 19 isolated rabbit hearts. In control of experiments on nine hearts perfusion with Tyrode solution with noradrenalin (10^{-6} M) led to quickening of HR by 48.4% (from 82.4 ± 5.5 to 120.3 ± 6.6 beats/min); the time taken for the response to develop was 6 ± 0.4 sec.

The effects of noradrenalin (10^{-6} M) preceded by perfusion for 15-20 min with Tyrode solution containing DSIP ($6 \cdot 10^{-6}$ M) were studied in experiments on 10 hearts. In these experiments the effect of noradrenalin accompanied by continuing perfusion with Tyrode solution containing DSIP was considerably depressed compared with the control: HR rose by only 29.3% (from 83 ± 6.1 to 105 ± 9.7 beats/min). The time for the response to develop was 6.5 ± 1.5 sec. Thus DSIP weakened the positive chronotropic action of noradrenalin on the heart by 19.1% ($p < 0.02$) compared with the control (Fig. 2).

In the modern view peptides are neuromodulators of various physiological reactions [1, 9]. It has been shown that DSIP has a marked modulating effect on neuronal activity in various brain structures [6]. However, there are no data in the literature on its action on the effects of mediators on the heart. Our own results show that DSIP enhances the negative chronotropic effect of acetylcholine and weakens the positive effect of noradrenalin. This action may be one of the mechanisms of the change in extracardiac regulation under the influence of this peptide.

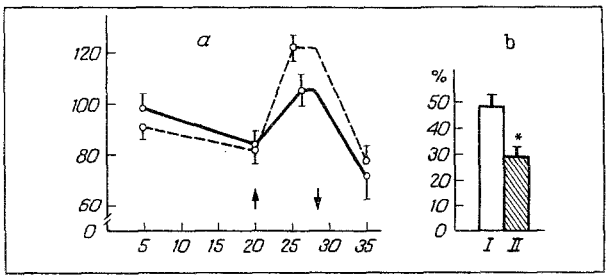

Fig. 2. Weakening of positive chronotropic effect of noradrenalin on isolated rabbit heart under the influence of DSIP. a: Broken line — time course of changes in HR under the influence of noradrenalin in hearts perfused with Tyrode solution; continuous line — the same for hearts perfused with Tyrode solution containing DSIP. Arrows indicate beginning and end of perfusion with noradrenalin solution; b) diagram characterizing increase in HR (in %) during the action of noradrenalin in control experiments (I) and under the influence of DSIP (II). $*p < 0.02$.

The authors are grateful to V. T. Ivanov and I. I. Mikhaleva for providing the delta sleep-inducing peptide, which was synthesized at the M. M. Shemyakin Institute of Bioorganic Chemistry, Academy of Sciences of the USSR.

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