PARASYMPATHETIC REGULATION OF THE HEART RATE IN DELTA-SLEEP PEPTIDE DEFICIENCY

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Delta-sleep peptide (DSP) has a marked antistress action [5-8]. In a study of the role of DSP in extracardial regulation of cardiac activity, the writers showed that it strengthens parasympathetic influences on the heart [2-4].

The aim of this investigation was to discover changes taking place in the parasympathetic regulation of the heart rate in animals deficient in DSP.

EXPERIMENTAL METHOD

Experiments were carried out on 35 chinchilla rabbits. Changes in the heart rate during the production of DSP deficiency were investigated in 15 unrestrained rabbits in a tranquil state. DSP deficiency was induced by means of an antiserum (titer 1:2000-1:3000), obtained from rabbits immunized with DSP. The antiserum was injected intravenously in a dose of 25 µl/kg (dilution 1:60). The specificity and effectiveness of this antiserum have been demonstrated by a number of investigators [9, 10]. Effects of vagus nerve stimulation before and after the creation of DSP deficiency were studied in acute experiments on five rabbits anesthetized with pentobarbital. The peripheral end of the left or right vagus nerve was stimulated for 30 sec. The vagal inhibition effect was assessed from the duration of the pause or the degree of slowing of the heart rate (HR) after electrical stimulation of the vagus nerve for 10, 20, and 30 sec respectively. The vagus nerve was stimulated by electrical pulses with a frequency of 100 Hz and a duration of 2-3 msec. The current strength was chosen to be a little above a threshold for obtaining a distinct vagal effect. Effects of vagus nerve stimulation were analyzed before and immediately after injection of the antiserum, every 15 min for 1.5-3 h. The ECG in standard lead II, blood pressure (BP), and the strength of the current used to stimulate the vagus nerve were recorded on the Mingograf-82. Control electron-microscopic investigations on the myocardium were carried out after production of DSP deficiency (nine rabbits), after injection of DSP in a dose of 60 nmoles/kg (nine rabbits) and also in six intact rabbits. To study the ultrastructure of the myocardium three animals were taken from each group 3 and 24 h and 6 days after receiving a single injection of antiserum or of DSP.

EXPERIMENTAL RESULTS

In the present experiments DSP deficiency led to a marked increase in HR. In 15 freely behaving rabbits a single injection of antiserum increased HR from 228.5 ± 10.8 to 326.7 ± 8.8 beats/min (by 48%, $p < 0.05$). The increase in frequency began after only 10 min and it reached a maximum 1.5-3 h after injection of the antiserum. HR gradually began to decrease 4-5 h after injection of the antiserum, and reached its initial value by the beginning of the 2nd day.

In four animals a second injection of antiserum in the same dose on the 2nd day caused virtually no change in HR. Meanwhile, if these animals were given a subsequent injection of DSP (60 nmoles/kg), which slowed the heart rate under ordinary conditions, after preliminary injection of the antiserum it had no negative chronotropic effect.

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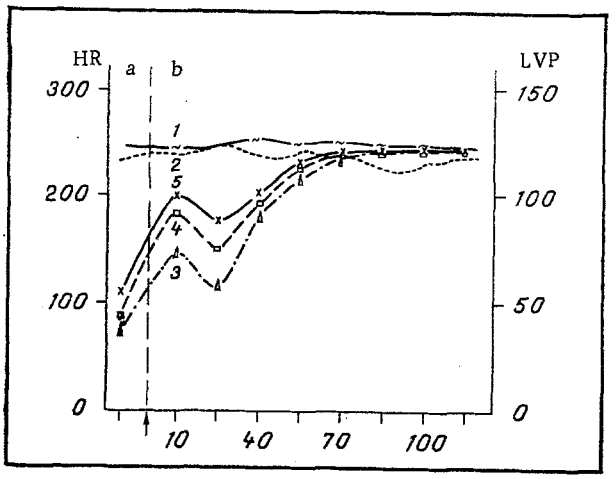

Fig. 1. Weakening of vagal inhibition of cardiac activity in a rabbit developing DSP deficiency. Abscissa, time after injection of antiserum (in min); ordinate: on left — HR, beats/min, on right — pressure in left ventricle (LVP, in mm Hg). 1, 2) HR (1) and LVP (2) before (a) and after (b) injection of antiserum; 3, 4, 5) HR during vagus nerve stimulation before (a) and after (b) injection of antiserum, after vagus nerve stimulation for 10, 20, and 30 sec respectively, repeated every 15 min for 1.5-2.5 h. Time of injection of antiserum indicated by arrow.

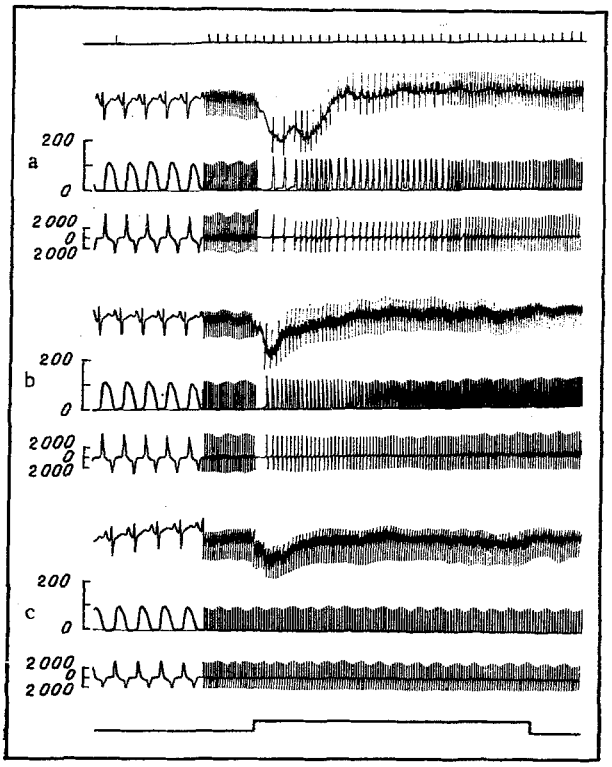

Fig. 2. Changes in chronotropic effect induced by vagus nerve stimulation in rabbits with DSP deficiency. a) Marked decrease in HR during control vagus nerve stimulation; b, c) progressive reduction of chronotropic effect during vagus nerve stimulation 20 and 60 min respectively after injection of antiserum. Legend for all traces: above — time marker, 1 sec, below — marker of vagus nerve stimulation; traces from top to bottom: ECG, LVP (in mm Hg), and its first derivative (in mm Hg/sec).

Effects of vagus nerve stimulation before and during the development of DSP deficiency were investigated in acute experiments on five rabbits. DSP deficiency was shown to have a marked effect on vagal inhibition of cardiac activity: it shortened the duration of vagal arrest of the heart and reduced the negative chronotropic effect (Figs. 1 and 2). The original HR in these experiments was 232 ± 30.6 beats/min and the average BP (BP_{av}) was 101.6 mm Hg. Against this background, control vagus nerve stimulation induced cardiac arrest for 3.2 ± 1.4 sec and had a marked negative chronotropic effect: 68.5 ± 41.1 beats/min (after stimulation for 30 sec). HR 1 h after injection of the antiserum showed no significant change (217.3 ± 33 beats/min, $p > 0.05$) and BP_{av} was 99.6 mm Hg. Under these circumstances cardiac arrest was shortened or disappeared, and the negative chronotropic action of the vagus nerve was reduced (to 158.6 ± 45.1 beats/min, $p < 0.05$) after stimulation of the nerve for 30 sec. The observed effect was independent of which vagus nerve (left or right) was stimulated.

Electron-microscopic investigation of the myocardium of nine animals showed that injection of DSP (60 nmoles/kg) caused virtually no changes in ultrastructure of heart muscle. No disturbances of myocardial ultrastructure likewise were found in six of the nine animals after injection of antiserum. However, in three animals which developed a marked, persistent sinus tachycardia (up to 330 beats/min) under the influence of the antiserum, a few damaged cells were observed in addition to intact cardiomyocytes on electron microscopy. Regions with overcontracted myofibrils, swelling of the mitochondria with partial destruction of their cristae, dilatation of the tubules of the sarcoplasmic reticulum, and the appearance of lipid inclusions were seen in them. These changes appeared after 3 h, they became more marked after 24 h, and disappeared 6 days after injection of the antiserum.

An essential condition for a proper interpretation of the action of peptides is the comparison of effects of their administration with those of their deficiency in the body [1]. As the writers found previously, intravenous injection of DSP into rabbits potentiates parasympathetic influences on the heart [3, 4]. It is of fundamental importance that this action of DSP has been confirmed also in investigations of animals with DSP deficiency.

According to our data, a single injection of antiserum causes marked quickening of the heart for 6-8 h. However, on the 2nd day after injection of antiserum normal cardiac activity as a rule is restored. This recovery of HR is evidently due to compensatory reactions and not to cessation of action of the antiserum. Evidence that it continues to have an effect is given by the fact that control injection of DSP under these conditions does not lead to reduction of HR, as it does in intact animals.

According to the results of the electron-microscopic investigation DSP deficiency in most experiments caused virtually no change in myocardial ultrastructure. If any such changes did arise, as a rule they were coupled with marked predominance of sympathetic influences on the heart, which led to characteristic disturbances of myocardial ultrastructure [8].

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