EFFECT OF DELTA-SLEEP PEPTIDE AND ITS DEFICIENCY ON SYMPATHETIC REGULATION OF THE CARDIAC RHYTHM IN VIVO

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Delta-sleep peptide (DSP) has a marked antistressor action [6, 8]. Investigation of the role of this peptide in extracardiac regulation showed that DSP potentiates parasympathetic influences on the heart [5, 9]. This also was confirmed by a study of the parasympathetic regulation of cardiac activity under conditions of DSP deficiency [4]. The aim of this investigation was to discover how sympathetic regulation of the cardiac rhythm changes under the influence of DSP administration and deficiency.

EXPERIMENTAL METHOD

The effect of DSP and its deficiency on stimulation of the stellate ganglion was studied in acute experiments on 16 rabbits. For this purpose, the animals were anesthetized with pentobarbital (40 mg/kg), artificial respiration was applied mechanically, and both stellate ganglia were dissected and bipolar silver electrodes were fixed to them. Both sympathetic nerves were divided at the level of the neck, and one of the sympathetic ganglia (mainly the right) was stimulated by square pulses 2-3 msec in duration and with a frequency of 30-50 Hz; the strength of the current was chosen so as to produce a marked sympathetic effect. The duration of each stimulation was 30 sec, and stimulation was applied every 15 min. The effect of stimulation was estimated by the maximal increase in heart rate (HR) during stimulation and during development of the sympathetic response. The stellate ganglia were stimulated before and after intravenous injection of DSP or its antiserum, over a period of 1.5-2 h.

DSP was injected intravenously in a dose of 60 nmole/kg [6, 7]. A deficiency of DSP was induced in animals with the aid of antiserum (T = 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 efficacy of this antiserum have been demonstrated by several workers [10, 11].

The ECG in standard lead II, arterial blood pressure, pressure in the left ventricle, and strength of the current applied to stimulate the sympathetic ganglia were recorded on a "Mingograf-82."

EXPERIMENTAL RESULTS

The effect of DSP on the effects of stimulation of the stellate ganglion was tested on six rabbits. In animals anesthetized with pentobarbital (40 mg/kg) the sympathetic nerves were divided bilaterally at the level of the thyroid cartilage of the larynx. Under these circumstances HR fell from 261.6 ± 9.6 to 186.0 ± 9.2 beats/min, pressure in the left ventricle (LVP) was 100 ± 5.8 mm Hg, and BP_{mean} was 86.4 ± 4.7 mm Hg. Against this background, stimulation of the stellate ganglion for 30 sec led to an increase in HR, by 47.3 beats/min (to 233.3 ± 5.1 beats/min). The time taken for this response to develop after the beginning of stimulation was 17.3 ± 1.0 sec.

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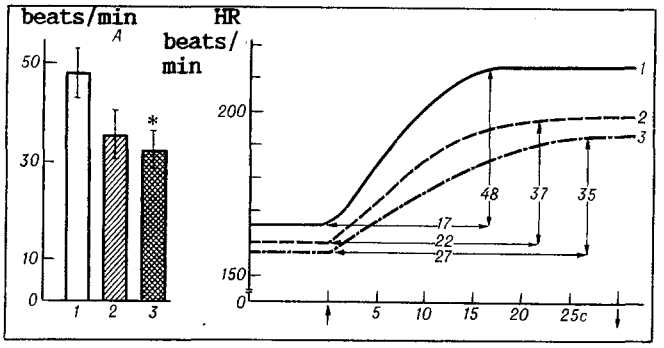

Fig. 1 Fig. 2

Fig. 1. Weakening of positive chronotropic effect on the heart during stimulation of stellate ganglion against the background of action of DSP. A) Increase in HR (in beats/min) during stimulation of stellate ganglion: 1) before, 2) 30 min after, and 3) 60 min after injection of DSP (60 nmoles/kg). *$p < 0.05$.

Fig. 2. Effect of DSP on rate of change of cardiac rhythm and on heart rate during stimulation of rabbit stellate ganglion. 1, 2, 3) Change in HR during stimulation of stellate ganglion before (1) and 30 min (2) and 1 h (3) after injection of DSP (60 nmoles/kg). The duration of stimulation of the stellate ganglion is marked by arrows. Number beneath curves: time taken for response to develop (in sec), horizontally; increase in HR (in beats/min), vertically.

HR 1 h after injection of the peptide was 195 ± 4.2 beats/min, LVP was 85 ± 7.1, and BP_{mean} 67 ± 6.7 mm Hg. In response to stimulation of the sympathetic ganglion there was a further decrease in the positive chronotropic effect: the rise of HR was 29.2 beats/min, $p < 0.05$ (up to 224.6 ± 4.4 beats/min) (Fig. 1). The time taken for it to develop increased to 23.3 ± 2.3 sec.

The time course of weakening of the sympathetic response to stimulation of the stellate ganglion under the influence of DSP in one experiment is shown in Fig. 2. Clearly the peptide weakened the effect of stimulation of the sympathetic ganglion: the increase in HR from 48 beats/min before injection of the peptide was reduced to 35 beats/min 1 h after its injection. The time taken for the sympathetic response to develop also was lengthened (from 17 to 27 sec).

In control experiments on five animals, instead of DSP, a mixture of the amino acids of the peptide in the same dose was injected intravenously. In these experiments there was no significant decrease in the positive chronotropic effect after injection of a mixture of amino acids compared with initial stimulation of the stellate ganglion. This is evidence that weakening of the sympathetic response to stimulation of the stellate ganglion is due to the action of the peptide itself, and not to the set of amino acids composing it.

These results also were confirmed by creating DSP deficiency in animals: intravenous injection of serum containing antibodies to the peptide (T = 1: 3000) into five rabbits gave the opposite effects. Against the background of the action of antiserum, the positive chronotropic effect to stimulation of the stellate ganglion increased compared with initial stimulation. For instance, whereas after initial stimulation of the stellate ganglion HR increased on average by 39.0 beats/min (from 190 ± 8.8 to 229 ± 6.4), 1 h after injection of the antiserum the increase in HR amounted to 51.4 beats/min (from 198 ± 7.1 to 269 ± 9.1).

DSP thus has a marked effect on sympathetic regulation of cardiac activity. Potentiation of parasympathetic influences on the heart by the action of this peptide in unanesthetized rabbits takes place not only because of an increase in vagus nerve tone [4, 5], but also as a result of weakening of sympathetic influences on the heart. One mechanism of this change in sympathetic regulation may be both the central action of DSP [5] and its ability to reduce the positive chronotropic effect of noradrenalin, as we found on the isolated heart [3, 9].

An essential condition for the correct interpretation of the action of peptides is a comparison of the effects of their administration and of their deficiency in the body [1]. It is therefore important in principle that the action of DSP on sympathetic regulation of the cardiac rhythm must be confirmed by creation of a deficiency of this peptide in the animal.

We showed previously that the protective action of DSP on cardiac activity during emotional stress is mediated not only through its central antistress action [2, 8], but also by potentiation of parasympathetic influences and normalization of the electrical stability of the heart [9]. Weakening of sympathetic influences on the heart following injection of DSP will evidently also be an important mechanism of the antistressor action of this peptide.

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