PHYSIOLOGY

Central and Peripheral Actions of Delta Sleep-Inducing Peptide on Electrical Stability of the Heart

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In rabbits under nembutal anesthesia delta sleep-inducing peptide injected intravenously or directly into a ventricle of the brain raised the threshold for ventricular fibrillation. Its effect on the electrical stability of the heart after central administration developed later than after systemic administration. Bilateral vagotomy did not alter the central effects of this peptide.

Key Words: *electrical stability of the heart; delta sleep-inducing peptide; systemic and intraventricular administration*

An important development in research on the physiological activity of delta sleep-inducing peptide (DSIP) was the discovery of its ability to alleviate stress. DSIP was found to make animals more resistant to emotional stress and to prevent their death from cardiovascular disorders [4]. Studies into the mechanisms of the antistress effect revealed that the peptide produces this effect primarily by acting on the brain [6]. When injected into a brain ventricle, it blocks the behavioral and autonomic manifestations of negative emotional reactions in various animals [2,6].

It has been established that the increased stability of cardiovascular functions shown by stressed animals administered DSIP is determined not only by its central action but also by its direct influence on the heart. For example, DSIP raises the thresholds for the elicitation of ventricular arrhythmias in intact animals, prolongs the effects of the vagus nerves on the heart and suppresses those of sympathetic nerves, and enhances or weakens, respectively, the effects of cholinergic and adrenergic transmitters [8]. Systemically administered DSIP normalizes the electrical stability of the heart and exhibits an antiarrhythmic effect in emotional stress [1,8].

Studies on the mechanisms of action of DSIP have thus demonstrated that central and peripheral effects can be produced by this peptide following its intracentral as well as intravenous administration. In view of the conflicting evidence regarding the permeability of the blood-brain barrier to DSIP [3,9,11] we compared in the present study the effects of DSIP on the electrical stability of the heart in rabbits after its intravenous injection with the effects after its injection directly into a brain ventricle. This work was undertaken to gain insight into the relationship between the central and peripheral mechanisms of DSIP action on the heart.

MATERIALS AND METHODS

Acute experiments were carried out on 28 male Chinchilla rabbits (body weight 2.0-2.5 kg) under Nembutal anesthesia (40 mg/kg). In 15 of the rabbits, the effect of DSIP on myocardial electri-

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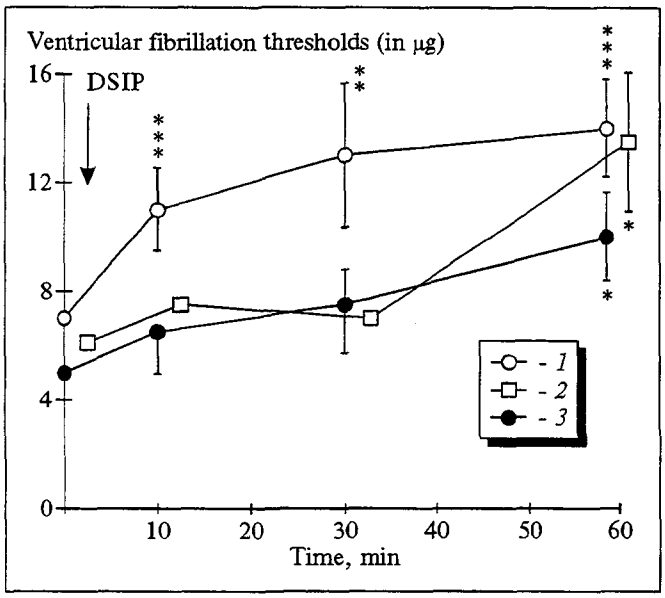

Fig. 1. Time course of variation of ventricular fibrillation thresholds following central or systemic administration of DSIP. *1*) Intravenous injection (60 nmol/kg); *2*) intraventricular injection (10 μg); *3*) intraventricular injection (10 μg) after bilateral vagotomy. One asterisk: $p<0.05$; two asterisks: $p<0.02$; three asterisks: $p<0.001$.

cal stability was assessed after its injection into the right or left lateral brain ventricle in a dose of 10 μg in 20 μl physiological saline. These microinjections were done with a Hamilton syringe via a special metal cannula. The results were compared with those obtained for the other 13 rabbits, in which we assessed the effect of DSIP on myocardial electrical stability after its intravenous injection in a dose of 60 nmol/kg. In 7 rabbits, bilateral vagotomy was performed 20-30 min before the intraventricular injection of the peptide in order to see what role the vagi might play in mediating its central influences on the heart.

Myocardial electrical stability was evaluated in rabbits maintained on artificial respiration by determining the threshold for ventricular fibrillation elicited by electrical pulses applied during the vulnerable phase of the cardiac cycle [12]. A series of 8 rectangular pulses of 5 msec duration each was delivered to the left ventricular epicardium after every 8-9 cardiac cycles (according to a program) using a biophase synchronizer with a 50-90 msec delay relative to the R wave of the electrocardiogram (ECG). The electrical current, which in each subsequent series of test pulses was 1.5 to 2.0 mA stronger than in the preceding one, was recorded with a Mingograph-82 cardiopolygraph synchronously with the ECG in the second standard lead and with the arterial and left ventricular pressures. The effect of DSIP on the ventricular fibrillation threshold was evaluated at minute 10 after the intravenous or intraventricular injection and then every 30 min for 2 h. The doses indicated above were selected on the basis of our own observations [1,8] and those of other authors [4,11]. The results were treated statistically using Student's *t* test.

The DSIP used in this study was synthesized in the M. M. Shemyakin Institute of Bioorganic Chemistry, Moscow, and kindly provided to the author by Associate Member of the Russian Academy of Sciences V. T. Ivanov and Senior Research Worker I. I. Mikhaleva.

RESULTS

In the group of 13 rabbits in which DSIP was studied for its influence on the ventricular fibrillation threshold after its intravenous injection (60 nmol/kg), this threshold had increased significantly from the baseline level of 7.2±0.8 mA to 11.4±1.1 mA ($p<0.01$) by minute 10 postinjection and to 13.4±2.4 mA ($p<0.02$) by minute 30, to remain at a high level (13.9±1.6 mA; $p<0.01$) at minute 60 postinjection (Fig. 1), and it remained elevated until the end of the test (minute 120). The heart rate and mean arterial pressure, which equaled 228±7.5 beats/min and 93.7±3.5 mm Hg before the injection, remained unchanged throughout the 120-minute period.

Thus, DSIP injected intravenously began to influence myocardial electrical stability after just a few minutes, and this effect reached its maximum at minutes 30-40.

In the group of 8 nonvagotomized rabbits in which DSIP was injected into a lateral ventricle in a dose of 10 μg, the ventricular fibrillation threshold had not changed significantly by the 10th or 30th minute postinjection (Fig. 1), its values at these times being 7.7±1.2 mA and 7.5±0.8 mA, respectively, vs. 5.6±1.1 mA before the injection. It was only 60 min postinjection that the threshold rose significantly to 12.5±2.9 mA ($p<0.05$). In these groups, too, the heart rate and mean arterial pressure both remained unchanged (their baseline values were 223±11.4 beats/min and 94.3±6.7 mm Hg).

In the group of 7 bilaterally vagotomized rabbits injected with DSIP intraventricularly, the pattern of variation in the ventricular fibrillation threshold was similar to that in the preceding group (Fig. 1). The threshold did not increase significantly until 60 min postinjection (from 4.9±1.2 mA before injection to 10.2±1.6 mA; $p<0.05$). The heart rate and mean arterial pressure remained unchanged, as they did in the other two groups (their

baseline values were 209.5±13.8 beats/min and 96.0±6.4 mm Hg).

Thus, DSIP injected into a brain ventricle directly raises the myocardial fibrillation threshold 60 min postinjection, an effect which is not affected by bilateral vagotomy.

Emotional stress can lead to various disturbances of the cardiac rhythm and may be responsible for sudden death from ventricular fibrillation [7,16], one mechanism of which is diminished electrical stability of the myocardium [13]. Measurement of this major indicator of cardiac function can provide very important information for evaluating the stability of cardiac activity under the action of various physiological or pathological agents.

This study has shown that DSIP raises the ventricular fibrillation threshold both after systemic and after central administration. However, after systemic administration the ventricular fibrillation increased significantly after 10-20 min and remained elevated throughout the observation period, whereas after central administration no significant increases in this threshold were recorded until the 60th minute. These findings indicate that the ability of DSIP to elevate the ventricular fibrillation threshold during the first 30-40 min after systemic, but not after central, administration is due to the fact that this peptide acts peripherally. The ability of DSIP to act on the myocardium directly was demonstrated previously in our experiments with isolated rabbit hearts [8]. Under conditions in which central influences are excluded completely, DSIP weakens the positive chronotropic effect of norepinephrine while enhancing the negative chronotropic effect of acetylcholine. That the peptide acts in this manner is also suggested by the reported wide distribution of DSIP-like immunoreactivity not only in various regions of the brain but also in peripheral organs and tissues [10,11].

As shown above, the peptide also increased the electrical stability of the heart when administered centrally, although with a delay of about 60 min. This effect may be explained by a central action of DSIP, primarily through extracardiac regulation. The electrical stability of the heart both in intact animals and in those under emotional stress has been shown to be strongly influenced by the state of sympathetic-parasympathetic interactions [5,7]. Stimulation of cardiac sympathetic nerves decreases myocardial electrical stability, whereas stimulation of parasympathetic nerves increases it [17]. DSIP enhances the action of the vagus nerves on the heart [8].

In our experiments, bilateral vagotomy did not alter the effects of DSIP on myocardial electrical stability after its injection into a lateral brain ventricle, which suggests that these effects are not mediated by the central component of parasympathetic regulation.

One of the mechanisms by which DSIP acts may be presumed to involve its overcoming the blood-brain barrier and its peripheral action. There is evidence that DSIP can cross the blood-brain barrier in both directions by transmembrane diffusion [9,15]. Further evidence that it can cross this barrier is provided by its central effects following peripheral administration [6] and by the isolation from venous blood of a DSIP elaborated by brain neurons [14]. The results of our study confirm this. On the other hand, it is possible that DSIP can raise the threshold of electrical stability of the heart by diminishing the sympathetic influences.

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