sprouting. Evidence that this is so is given by the presence of thin processes on terminal segments of first-order neurites, which have undergone retraction, in some cases (Fig. 3).

It can be concluded from these experimental data that cells of a mechanosensory neuron may respond to elimination of cells of the same modality by retraction of their processes after a short time. The neuron net is evidently a dynamic structure, reorganizing itself in response to death of some of its cells.

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EFFECT OF SUBSTANCE P AND ITS FRAGMENTS ON PHYSIOLOGICAL AND PATHOLOGICAL PAIN

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Among the neuropeptides with an antinociceptive effect, a special place is occupied by substance P (SP). As a neurotransmitter of primary sensory neurons, it participates in the transmission of nociceptive impulsation, and at the same time, it possesses regulatory properties, and under certain conditions it depresses pain responses [2-6]. To explain this, at first glance, paradoxical phenomenon, several suggestions have been made. Some workers consider that large doses of SP induce depolarization of the postsynaptic membrane, which has an algesic effect, whereas small doses have an analgesic effect through the release of endogenous opioid peptides from presynaptic endings [2]. Other workers consider that the effect of SP depends on the initial state of the recipient, on binding of SP and (or) its fragments with receptors of various types [3, 4]. Investigations in recent years have revealed spatial demarcation of functions in the SP molecule, and the promising nature of the study of biological effects of SP fragments.

The aim of this investigation was to study the effect of SP and its fragments on physiological and pathological pain.

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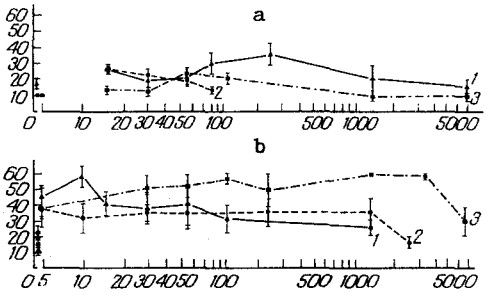

Fig. 1. Effect of SP and its fragments SP_{1-4} and SP_{5-11} on LP of pain response of rat to nociceptive thermal stimulation when injected intraperitoneally (a) and given by microinjection into dorsal nucleus raphe (b). Abscissa, time of observation (in min, logarithmic scale); ordinate, values of LP (in sec). 1) SP, 2) SP_{1-4}, 3) SP_{5-11}.

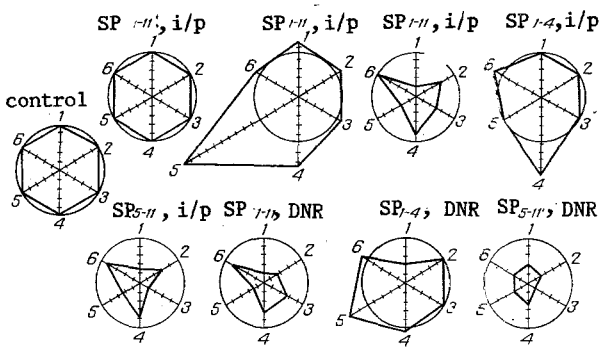

Fig. 2. Effect of SP and its fragments on pain syndrome of spinal origin. Quantitative values of six components of pain syndrome displayed on line and circle diagrams. Center of circle represents zero point of ordinates, radius of circle represents ordinate of one component, intensity of each component expressed as a percentage of initial value. Numbers correspond to components of pain syndrome: 1) vocalization, 2) general motor activity, 3) frequency of seizures, 4) duration of seizures, 5) local response, 6) response to stimulus. Control) before injection of substance; i/p) after intraperitoneal injection of substances; DNR) after microinjection of substances into dorsal nucleus raphe.

EXPERIMENTAL METHODS

Experiments were carried out on male Wistar rats weighing 200-250 g. To study the effect of SP and its fragments on physiological pain, the hotplate test was used. By means of this test the latent period (LP) of the full pain response, consisting of several components, to nociceptive thermal (55°C) stimulation, which, in the absence of response, was continued for not more than 60 sec, was determined.

To study the effect of SP and its fragments on pathological pain a model of the pain syndrome of spinal origin was used. This syndrome was induced in rats by creating a generator of pathologically enhanced excitation in the posterior horns of the lumbar division of the spinal cord by application of an agar slab (1.5 × 3 × 6 mm) containing penicillin in a concentration of 7.5 U/mm^3 [1]. Six components of the spinal syndrome were evaluated: vocalization, the general motor response, frequency of seizures, the duration of the seizures, local response, and response to stimulus, using a 3-point scale. SP and its fragments (SP_{1-4} and SP_{5-11}) were diluted immediately before the experiment, with observance of all the special features of dilution of this peptide. For intraperitoneal injection equimolar doses were used: SP 250 μg/kg, SP_{1-4} 107 μg/kg, and SP_{5-11} 141 μg/kg. Microinjections of peptides into

the dorsal nucleus raphe in a volume of 3 μl (dose 3 μg) were given through cannulas inserted beforehand into this nucleus.

The significance of differences was determined by Student's test.

EXPERIMENTAL RESULTS

A significant increase in LP ($p < 0.01$) was observed 30 min after intraperitoneal injection of SP_{1-4} (Fig. 1a) and the analgesic effect lasted 30 min. Analogous injection of SP_{5-11} (Fig. 1a) also induced a significant increase in LP after 60 min ($p < 0.01$). The effect continued for the next 60 min, and in some animals even longer. Injection of the undecapeptide caused suppression of the pain response with a latent interval of 60 min. Injection of the control solution caused no significant changes in LP.

Microinjections of the peptides into the dorsal nucleus raphe was accompanied by depression of the pain responses to thermal stimulation. A significant increase ($p < 0.001$) in LP was observed immediately after microinjection both of the SP peptide and of its fragments, but the intensity and duration of the analgesic effect differed. Fragment SP_{5-11} had the strongest and most prolonged effect; in this case LP of some rats remained longer than initially even on the 5th day after injection (Fig. 1b).

Microinjections of the control solution into the dorsal nucleus raphe were accompanied by transient changes in LP of the nociceptive responses during the first 5 min.

When injected intraperitoneally into rats with a spinal pain syndrome, SP differed in its effects on the course of the pain syndrome of spinal origin. In some rats injection of the peptide was accompanied by intensification of the syndrome, whereas in others, a phase of depression of the syndrome was observed after 20-30 min, and in a third group, injection of the peptide had no appreciable effect on the course of the syndrome. When injected into rats with a spinal syndrome, SP_{1-4} caused disappearance of the clear pain projection, the rats became more aggressive, and no depression of the components of the syndrome was observed. A similar injection of SP_{5-11} changed the structure of the pain syndrome: initially vocalization was suppressed, and the motor response during the period of the seizure was depressed by a lesser degree (Fig. 2).

Microinjections of SP and its fragments into the dorsal nucleus raphe gave rise to dissimilar changes in the structure of the syndrome, reducing only one of its components, whereas certain others were actually enhanced. SP_{1-4} had little effect on the structure of the syndrome, lessening only one component, and even increasing several others. After microinjection of SP, depression of five components of the syndrome was observed, and depression of vocalization was the most marked effect. After microinjection of fragment SP_{5-11} into rats with a spinal syndrome, all components of the latter were considerably depressed immediately after injection of the substance, and recovery of the initial parameters of the syndrome was not observed (Fig. 2).

Thus the data are evidence that SP and its fragments, under certain conditions, induce an analgesic effect against both physiological and pathological pain. It must be pointed out that the hypoalgesia induced by injection of these peptides possesses certain special features. A long latent period after intraperitoneal injection was found, with absence of this interval in the case of microinjection of the peptide into the dorsal nucleus raphe; the effect was significantly stronger after microinjection into the dorsal nucleus raphe, and the course of analgesia after a single injection of the peptide was prolonged. The following relationship was found between the intensity of the analgesic effect and the peptide injected: $SP_{5-11} > SP_{1-11} > SP_{1-4}$ (in the case of microinjection into the dorsal nucleus raphe), and $SP_{5-11} > SP_{1-11}$ (by the intraperitoneal method of injection).

These results are evidence that clear and prolonged hypoalgesia arises when SP or its fragments are injected into the dorsal nucleus raphe – a structure of the antinociceptive system. This analgesic effect may arise on account of activation of the antinociceptive system when acted upon by SP and (or) its fragments.

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SPIKE ACTIVITY OF BULBAR RESPIRATORY NEURONS IN CATS WITH MYOCARDIAL ISCHEMIA: MICROELECTRODE STUDY

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Clinical data are evidence of changes in respiratory function when the coronary blood flow is disturbed [9, 14]. It has been shown experimentally that changes in activity of some types of respiratory neurons of the ganglion nodosum and neurons of the respiratory center take place in response to compression of the coronary vessel [4, 6]. It can be tentatively suggested that the cause of the respiratory disturbances in these patients may be the modified character of afferent signals reaching the CNS in acute myocardial ischemia.

In this investigation the spike discharge of different types of respiratory neurons in the medulla was studied at different stages of myocardial ischemia.

EXPERIMENTAL METHODS

Experiments were carried out on 45 cats weighing 2.5-4 kg under pentobarbital anesthesia (30-40 mg/kg, intraperitoneally) with artificial respiration. Electrical activity of the respiratory neurons was recorded extracellularly with the aid of glass microelectrodes, filled with 2.5 M KCl. The neurons were identified by stereotaxic coordinates: 2-4 mm laterally and 3 mm rostrally and caudally to the level of the obex [7]. Myocardial ischemia was induced by compression of the circumflex branch of the left coronary artery by means of an adjustable loop for a period of not more than 15 min. In all experiments neuronal activity, the ECG in standard lead I or II, the blood pressure by the direct method in the coronary artery, using an EMT-35 electromanometer (Elema, Sweden), and the pneumogram by means of an EMT-32C transducer (Elema) were recorded continuously. The recorded signals were amplified on a M-42 four-channel myograph (Medicor, Hungary) and recorded on a four-channel SDR-41 tape recorder (Nihon Kohden, Japan) and on 70 mm RF-3 film by means of a four-channel MR-4 photographic recorder (Medicor). Spontaneous neuronal activity was processed manually and by ES 1020 or Iskra 226 computer, using a specially written program for statistical analysis. The character of activity of the respiratory neurons during the experimental procedure was determined over six respiratory cycles, with respect to the following parameters: number of spikes per burst (N), duration of the burst (T), and average spike frequency in the burst (F). The pH and gas composition of the arterial blood were measured before and after ligation of the coronary vessel, in the early (measurement of the ST interval on the ECG) and late (deformation of the QRS complex on the ECG) stage of myocardial ischemia. Values of pH, pO_2, and pCO_2 were determined by means of the micro-Astrup MBS 3Mk2 system (Radiometer, Denmark). The data were subjected to statistical analysis by Student's t test and the chi-square test.

EXPERIMENTAL RESULTS

Activity of 57 bulbar respiratory neurons was recorded: 27 inspiratory, 18 inspiratory-expiratory, 3 expiratory, and 9 expiratory-inspiratory. Activity of the respiratory neurons was analyzed with respect to ECG changes in the early and late stages of myocardial ischemia, when the cardiac rhythm was disturbed.

It will be clear from Fig. 1 (stage 1) that the inspiratory neurons changed their firing pattern after compression of the coronary vessel, even before the development of ischemic

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