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EFFECT OF DALARGIN ON THE HEMODYNAMICS OF ANESTHETIZED RATS AFTER TRUNCAL VAGOTOMY

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Dalargin, a synthetic Leu-enkephalin analog, has been successfully used in combination with measures of anesthesiologic protection during various types of surgical operations [1, 5, 6, 8]. Dalargin effectively stabilizes the hyperdynamic response of the circulation to a supramaximal nociceptive stimulus [9], and the addition of an opioid peptide to the program of combined general anesthesia has led to a substantial decrease in the amounts of general anesthetics used during operations on the abdominal organs without any detrimental effect on the quality of the anesthesia [2, 7]. General anesthesia with dalargin also was characterized by lower values of total peripheral resistance at the traumatic stages of the operation compared with patients undergoing surgery under neuroleptanalgesia. This phenomenon may probably be the result of the depressant effect of dalargin on the autonomic nervous system. However, we have noted that atropine, if given as a component of premedication, leads to some impairment of the course of combined general anesthesia with dalargin, manifested sometimes as the development of moderate arterial hypertension, frequently unconnected with traumatic stages of the operation.

The aim of this investigation was to study the effect of dalargin on the hemodynamics of anesthetized rats after bilateral frontal vagotomy and in response to nociceptive stimulation.

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EXPERIMENTAL METHOD

Experiments were carried out on 29 noninbred male albino rats weighing from 250 to 310 g. Under pentobarbital anesthesia (40 mg/kg, intraperitoneally) tracheostomy was performed on the animals and artificial ventilation of the lungs instituted with the DAM-64 apparatus, operating on a program of moderate hyperventilation (respiratory volume 2.5-2.7 ml, respiration rate 68-70 cycles/min). For administration of the dalargin the right jugular vein was catheterized with "Viggo" venous cannulas (France). The cardiac output was determined by means of a "Nihon Kohden" electromagnetic flowmeter (Japan), the transducer of which was fixed to the ascending arch of the aorta. To measure the aortic pressure laparotomy was performed and the abdominal aorta was exposed and catheterized with a "Viggo" arterial cannula (France). The tracheostomy skin incision was widened and the trunks of the vagus nerves were isolated and divided bilaterally. A nociceptive stimulus of measured duration and strength was applied. A hyperdynamic response of the circulation was regarded as a positive response to nociception. All tests were carried out under total myoplegia with Arduan (pipecuronium bromide) in a dose of 0.1 mg/kg. The cardiac output (CO) and blood pressure (BP) were recorded on a "Salyut" polygraph (USSR). The following hemodynamic parameters were calculated: average BP (BP_{av}), stroke volume (SV), cardiac index (CI), stroke index (SI), total peripheral resistance (TPR), power of the left ventricle (PLV), and the double product (HRP). The hemodynamic parameters were tested at the following stages: 1) initial state, 2) after bilateral vagotomy, 3) at the peak of the hyperdynamic response, and 4-7) 20 sec, 60 sec, 120 sec, and 240 sec respectively after injection of dalargin. A group of animals not undergoing vagotomy served as the control. The results were subjected to statistical analysis by Student's paired t test.

EXPERIMENTAL RESULTS

In rats not vagotomized injection of dalargin at the peak of the hyperdynamic response led after 60 sec to reduction of HR by 7% ($p < 0.001$) (relative to its initial level HR was 100.1%), of BP_{av} by 16.9% ($p < 0.001$) (relative to its initial level 98.2%), of CI by 14.6% ($p < 0.001$) (relative to its initial level 100.3%), and TPR by 11.2% ($p < 0.001$) (relative to its initial level 97.8%). It will be clear from the data given above that dalargin in a dose of 25 μg/kg completely abolished the hyperdynamic response of the circulation and returned the parameters studied to their initial levels, despite continuing nociceptive stimulation. The peak of the action of the peptide in the above-mentioned dose was observed between 55 and 110 sec after its injection. A second "wave" of hyperdynamic response was observed 115-120 sec after the single injection of dalargin (against the background of continuing stimulation). The peak of the second "wave" was observed 240-250 sec after injection of the opioid. Under these circumstances HR was 6.6% higher than initially ($p < 0.001$), and amounted to 99.5% of its value in the first "wave" of the hyperdynamic response, BP_{av} was 14.1% higher ($p < 0.001$) (97.6% of the value in the first "wave"), and CI 13.7% greater ($p < 0.001$) (99.1% of its value in the first "wave"). The mu-opioid agonist fentanyl caused similar changes in the hemodynamics. The main difference was that the action of the latter was more prolonged.

Bilateral truncal vagotomy caused an increase of HR by 4.6% ($p < 0.01$) relative to its initial level, and as a result, there was a moderate increase of CI by 1.9% ($p > 0.05$), whereas there was no significant change in the level of BP_{av}. The nociceptive stimulus led to a further increase in HR by 3.9% ($p < 0.01$), CI by 12.7% ($p < 0.001$), and BP_{av} by 17.1% ($p < 0.001$) compared with the previous stage of the investigation. Injection of dalargin in the standard dose caused changes in the hemodynamics similar to those in the control group. This state of affairs applies only to the time course of HR and CI. These parameters returned after 55-60 sec to the level in the second stage of the experiment (the state after vagotomy). However, the level of BP_{av} corresponded to hyperdynamic, and showed no significant deviation before the end of the experiment. The repeated "wave" began 100-105 sec after injection of dalargin and reached a maximum after 270-280 sec. Injection of dalargin (20 μg/kg) into the anesthetized, relaxed rats caused transient inhibition of the hemodynamics. For instance, 20 sec after injection of the peptide the following changes were found in the parameters: lowering of HR by 3.6% ($p < 0.001$), of BP_{av} by 10.5% ($p < 0.001$), and of CI by 0.8% ($p > 0.1$). Slowing of HR led to a small but not significant reduction of CI, but not of SI, and reduction of TPR by 11.6% ($p < 0.05$) caused changes which were in the same direction: in BP_{av} by 12.5% ($p < 0.05$) and in PLV by 8.8% ($p < 0.05$). Reduction of the load against which the left ventricle was working led to reduction of HRP at that stage by 14.0% ($p < 0.001$). There are thus no grounds for considering that dalargin, in the dose used, has a depressive action on the myocardium. The results described above are probably due to a change in the after-load. Bolus injection of the opiopeptide in a dose of 20 μg/kg into animals with truncal vagotomy

caused moderate depression of the hemodynamic parameters: HR was reduced by 3.3% ($p < 0.02$), CI by 8.9% ($p < 0.01$), and SI by 5.9% ($p < 0.01$), with a compensatory rise of TPR by 11.9% ($p < 0.02$), manifested as a small and not significant increase in BP_{av}. The trend of the changes in HR and BP_{av} in animals without vagotomy is in agreement with results obtained by other workers studying synthetic enkephalins and their effect on the basic parameters of the hemodynamics [3]. These changes are reflex in character and mediated by activation of opioid receptors, associated with vagal afferents of the lungs [4]. According to our data, the hemodynamic effects of dalargin were much weaker. Attention is drawn to the stability of BP and the moderate reduction of SV in response to injection of this peptide into vagotomized animals.

The protective properties of dalargin, including its depressant action on the autonomic nervous system, are thus partially realized by interaction with peripheral opioid receptors, activating the central component of the opioid anti-nociceptive system. A mechanism of direct action of dalargin or of its tetra- and pentapeptide fragments on specific "targets" of the CNS under conditions of operative stress, total myoplegia, and general anesthesia, also is possible. Bilateral truncal vagotomy also reduces the intensity of the protective effect of the neuropeptide on a model of surgical stress.

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