remains rather lower than in the control. Therefore, AMD prevents the blockade of the AC adrenosensitivity induced by the perfusion disturbances. It may be assumed that AMD affects the receptor-conjugated link. An elevated level of the contractile function of the perfused heart seems to be associated with the stimulation of the adrenergic mechanism due to the suppression of intracellular regulator synthesis.

To confirm the possible presence of factors inhibiting the adrenosensitivity of cells under conditions of long-time perfusion experiments were carried out to create *in vitro* "plasmalemma-cytosol" hybrids. Cytosols from hearts in various functional states, among them cytosols from animals injected preliminary with AMD, were used to ascertain the nature of the factors tested.

The results obtained show that during a direct reaction the control cytosols (14-th of perfusion) do not affect either the basal or stimulated AC activity of the intact heart membrane. At the same time, cytosols from cells of long-time perfused hearts have a weak inhibitory effect on the basal AC activity and a pronounced one on the adrenostimulated activity. Preliminary AMD injection completely eliminates the inhibitory effect of cytosols from cells of the long-time perfused heart both on the basal and adrenostimulated AC activity.

Therefore, the experiments carried out attest to the appearance in cytosols from myocytes of the long-time perfused heart of factors inhibiting the heart adrenosensitivity due to the suppression of AC adrenoreactivity. The inhibitory effect of the transcription inhibitor AMD on their synthesis testifies to their protein (peptide) nature. The findings allow us to conclude that the factors examined belong to the class of invertors - cell regulators, which transmit a control signal from the genome to the nucleus.

REFERENCES

1. L. N. Belov and L. I. Haustova, *Byull.Eksp.Biol.*, **72**, № 8, 110-114 (1971).
2. E. A. Demurov, L. I. Vinnitskii, N. I. Vasil'eva, *et al.*, *Kardiologiya*, № 6, 50-54 (1982).
3. F. Z. Meerson, *Pathogenesis and Prevention of Stress Damage to the Heart* [in Russian], Moscow (1984).
4. G. T. Sazontova, *Byull.Eksp.Biol*, **102**, № 11, 685-687 (1986).
5. V. A. Tkachuk, *Biol.Nauki*, № 6(282), 6-17 (1987).
6. V. V. Frol'kis, *Aging and Prolongation of Life* [in Russian], Leningrad (1988).
7. V. V. Frol'kis and A. L. Shkapenko, *Dokl.Akad.Nauk*, **315**, № 1, 249-251 (1991).

Role of the Sympathetic and Parasympathetic Nerves in the Development of Vagotomic Tachycardia

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Heart rate acceleration developing after vagus nerve switch off provides evidence that the vagus centers are always in a state of excitation that is termed tone [2]. Changed tone of the vagus nerve may have different effects on the work of the heart, either accelerating or decelerating. The constant tonic efferent activity of the vagus [11] and the development or persistence of developed vagotomic and atropine tachycardias after surgical or drug (propranolol or rausedil) switch off of the sympa-

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thetic nervous system [2] are also indicative of vagus tone. Some authors dispute the current notions on the inhibitory tone of the vagus [1,3, 5,7]. They claim that it is not the switch off of the vagus inhibitory tone which is responsible for vagotomic tachycardia, but rather stimulation of the sympathetic nervous system. Electrophysiological experiments on cats have revealed stellate ganglion stimulation starting 1-2 min after vagotomy and reaching the maximum in 30-40 min [3]. Stimulation of the sympathetic nervous system developing after vagotomy results, according to these authors [3,5,7], from heart deafferentation in vagotomy and from the cessation of afferent signaling about cardiac activity to the CNS. Such a conclusion is confirmed by some data [9] that the vagus nerves contain 14-15 times more afferent fibers than efferent ones. The sympathetic origin of vagotomic tachycardia was confirmed by experimental findings showing that pharmacologic blocking of the sympathetic nervous system (propranolol, 2 mg/kg) markedly reduced atropine tachycardia in cats, but propranolol by itself considerably decreased the heart rate - from 195 to 159 beats/min [12]. Similar results with pharmacologic desympathization were obtained in experiments with dogs: inderal in a dose 1.0-1.5 mg/kg sharply reduced both the vagotomic and atropine tachycardias, no matter when the drug was injected, before vagotomy and atropine injection or after these [2]. In these experiments as well inderal by itself strongly (by 23%) reduced the heart rate. Therefore, the discrepancy in these facts and opinions prompted us to proceed with this research.

Our aim was further study of the vagus tone and its contribution to heart work regulation; for this it was necessary to elucidate the main cause of vagotomic tachycardia: switch off of the inhibitory effect of the vagus on heart work or stimulation of the sympathetic nervous system?

MATERIALS AND METHODS

Experiments were carried out with 30 pigeons, 8 rats, and 9 cats under urethan anesthesia (1.5-2 mg/kg intraperitoneally for rats and cats or intramuscularly for pigeons). In the pigeon and rat experiments ECG or arterial pressure was recorded, while in the cat experiments left ventricular pressure and its right derivative $\Delta P/\Delta t$ were recorded. The latent time of vagotomic tachycardia in cats and pigeons (time from the moment of vagotomy till the onset of increased heart rate) was assessed from the moment of manifestation of a 10% reduction of the ECG R-R interval with the aid of a device specially designed by us for this purpose, which provided a simultaneous

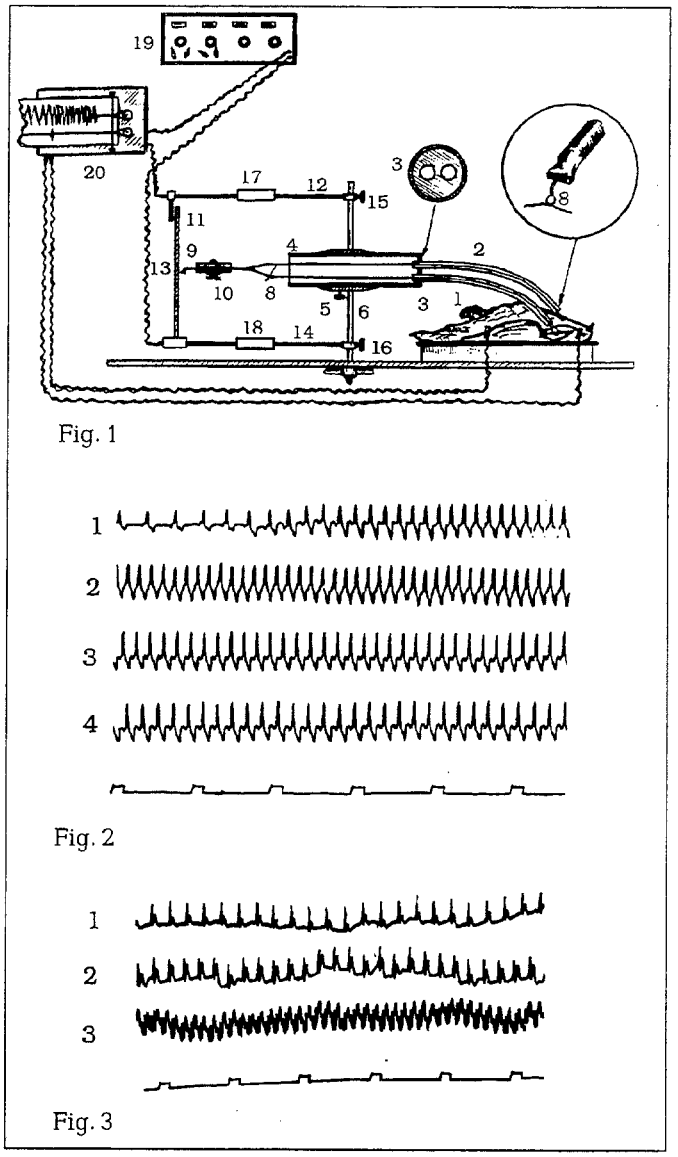

Fig. 1. A device for simultaneous cutting of two nerves and signal transmission to the recorder. 1, 2) tubular cutting elements; 3) collar into which the cutting elements are screwed; 4) tube; 5, 6, 7) fixing elements; 8) wire loop; 9) coupling; 10) nut; 11–18) electric circuit elements providing transmission of electric signal from stimulator 19 to recorder 20 during nerve cutting, which is realized by movement of wire loop 8 and pressing of the nerves to sharp edges of cutting elements.

Fig. 2. Changes of heart rate in a rat. 1) initial heart rate; 2) after ornidin injection – no changes; 3) after cutting of both vagus nerves in the presence of ornidin – increased heart rate. ECG recording in all fragments. Time mark 1 sec.

Fig. 3. Tachycardia latent time and velocity of heart rate augmentation in a pigeon after bilateral vagotomy. ECG recording in all fragments: 1) background (beginning of fragment) and after simultaneous bilateral vagotomy (the moment of vagotomy is shown with an arrow); 2) 5th to 10th min after vagotomy; 3) 4th min; 4) 10th min after vagotomy. Time mark 1 sec for all fragments (bottom line).

cutting of both vagus nerves and transferred the signal to the recorder (Fig. 1). Artificial respiration (AAR-3) was used in half the experiments in order

to stabilize gas exchange and rule out the effect on the heart rate of the hypoventilation developing after vagotomy due to laryngospasm. Tracheostomy was found sufficient in the other experiments. In such cases labored respiration became easier and sufficient for normal gas exchange. The parasympathetic nervous system was switched off with methacin (2-3 mg/kg i.m.) or by vagotomy, and the sympathetic nervous sytem with ornidin (20-30 mg/kg), which prevented catecholamine release by the sympathetic terminals, and with inderal, a β-adrenoreceptor blocker (2-3 mg/kg i.m.).

RESULTS

The first stage of research revealed in control experiments with 8 rats and 7 pigeons that preliminary switch off of the sympathetic nervous system with ornidin in anesthetized rats (Fig. 2) did not prevent the development of vagotomic tachycardia: their heart rate after ornidin injection was 317±19 beats/min and increased still more after bilateral section of the vagus nerves to 424±6 beats/min (34%, $p<0.001$). Methacin switch off of the vagus nerves in alert pigeons (without operative interventions) induced an increase of the heart rate from 147±9 to 389±33 beats/min (165%, $p<0.01$), and subsequent blocking of the sympathetic nervous system with inderal reduced the heart rate to 366 beats/min, that is, by only 6% ($p>0.05$). These findings permitted us to suppose that stimulation of the sympathetic nervous system recorded by some authors [3] in cats was not responsible for vagotomic tachycardia.

To verify this hypothesis, at the second stage of our research we attempted to find out the exact time of tachycardia onset after vagotomy (the latent period of vagotomic tachycardia) in pigeons and cats, for it is known that sympathetic nervous system stimulation in cats starts 1-2 min after vagotomy and peaks after 30-40 min [3]. A noteworthy fact is that a decrease of the heart rate was observed in these experiments directly after vagotomy. Of course, it was necessary to detect the cause of the inhibitory effect. The kymogram of one of the 15 experiments carried out with 15 animals illustrates the results of our investigations on estimation of the latent time of vagotomic tachycardia in pigeons (Fig. 3). It is seen that after vagotomy the heart rate started to rise as early as after the first cycle of cardiac activity with the latent time 0.31 sec (Fig. 3, *1*) and increased within the first second from 174 to 238 beats/min (if the heart persisted contracting for another minute at the same rate as in the first second). The maximal increment of heart rate was observed in the first 4 sec and constituted 51.4 beats in one second, as a result of which at the fourth second the heart rate was 380 beats/min. The rate increase from the fifth to the tenth second inclusive was several times lower (Fig. 3, *2*) being only 5.5 beats per second. The heart rate then remained virtually unchanged for 6 h, after which it started to drop, being 360 beats/min 4 min later (Fig. 3, *3*) and 321 beats/min in 6 more min (Fig. 3, *4*). According to the findings of the total series of experiments, the latent time of vagotomic tachycardia was 0.29±0.01 sec. Similar experiments were carried out with cats. Vagotomic tachycardia latency was 1.32±0.49 sec, as shown by 9 cat experiments. As for the heart rate reduction which developed in cats immediately after vagotomy in experiments of other scientists [3], our findings show that it results from mechanical stimulation of the vagus nerves by section. In our experiments, due to a specially designed device (Fig. 1), mechanical injury of the nerve or its stretching during cutting were ruled out; heart rate reduction did not occur either. On the other hand, mechanical stimulation of the vagus nerve or its stretching naturally did inhibit the heart rate in experimental animals (cats and rabbits).

Thus, the latent time of vagotomic tachycardia (0.29±0.01 sec in pigeons and 1.32±0.49 sec in cats) is hundreds of times shorter than the latent time of the sympathetic nervous system excitation (1-2 min in cats) recorded by some authors [3] after bilateral vagotomy, that is, tachycardia develops much sooner than sympathetic nervous system excitation starts. These experiments have demonstrated that vagotomic tachycardia latency in different animals depends on the degree of vagus tone manifestation: the more the tone is expressed, the shorter is the latent time of vagotomic tachycardia. These facts prove that the switch off of the vagus inhibitory tone is responsible for vagotomic tachycardia, rather than the sympathicus excitation.

Erroneous interpretation of the effects of a number of other factors, reducing by themselves the vagus nerve tone, such as muscular activity of emotional stress, may also lead to unjustified conclusions about the absence of vagus tone.

Some authors [5] report that in the fish fixed in a stand vagotomy was associated with tachycardia development, whereas in swimming fish vagotomy did not accelerate heat rate; this brought the authors to the unjustified conclusion of the absence of vagus tone in the fish. We contend that swimming was associated with a heart rate increase resulting from reduced tone of the vagus, and therefore vagotomy did not induce the usual tachycardia in these animals.

The findings of investigations carried out with various fishes (cod, plaice, father-lasher, skate) support this

conclusion: atropine injections (0.2-1.0 mg/kg), switching off the descending inhibitory effects, induced tachycardia [8]. Atropine injection (1 mg/kg in the pericardial cavity) in an anesthesized crucian carp increased the heart rate 2.1 times on the average and eliminated the variability of the diastolic intervals [10].

Emotional stress, as was shown in another series of our experiments, may also cause a significant reduction of vagus tone; this is demonstrated by the comparatively low increment of the heart rate in 8 alert pigeons after they were injected with atropine in a state of some agitation: from 242±14 to 340±28 beats/min (41%, $p<0.001$) as against the marked increase of the heart rate in 7 pigeons at rest (from 161±9 to 374±33 beats/min, 133%, $p<0.001$).

Thus, previous notions on vagus nerve tone and its role in heart work regulation are valid. At rest the sympathetic nervous system tone is virtually not manifested. Inadequate conditions for the detection of vagus tone have been responsible for variable outcomes of experiments carried out by different researchers. Different interpretations of the same facts have also contributed to the formation of erroneous conclusions.

REFERENCES

1. T. N. Kalishevskaya and M. G. Nikol'skaya, *Biol. Nauki*, № 7, 35-39 (1974).
2. G. P. Konradi, "The significance of efferent innervation of the heart", in: *Circulation Physiology. Heart Physiology* [in Russian], Leningrad (1980), pp. 400-411.
3. M. G. Nikol'skaya, G. E. Samonina, and M. G. Udel'nov, *Fiziol. Zh. SSSR*, **60**, № 10, 1557-1562 (1974).
4. M. G. Nikol'skaya, G. E. Samonina, and M. G. Udel'nov, *Ibid.*, **61**, № 10, 1449-1453 (1975).
5. G. E. Samonina, V. N. Kamenskaya, and M. G. Udel'nov, in: *Comparative Neurophysiology and Neurochemistry* [in Russian], Leningrad (1976), pp. 50-56.
6. M. G. Udel'nov, *Nervous Regulation of the Heart* [in Russian], Moscow (1961).
7. M. G. Udel'nov, *Physiology of the Heart* [in Russian], Moscow (1975).
8. I. A. Shparkovskii, in: *Physiology and Biochemistry of Neurotransmitter Processes* [in Russian], Moscow (1980), p. 229.
9. E. Agostony, Y. E. Chinnock, and B. N. Daly, *Physiol.*, **135**, № 1, 182-205 (1957).
10. John S. Cameron, *Comp. Biochem. Physiol.*, **63**, № 2, 341-349 (1979).
11. F. G. Katona, J. Poitras, O. Barnett, *et al.*, *Amer. J. Physiol.*, **218**, № 4, 1030-1037 (1970).
12. G. E. Samonina and M. O. K. Hakumoki, *Scand. J. Clin. Lab. Invest.*, **43**, № 5, 389-392 (1983).

Serotonin-Producing Cells in Eu- and Hypothermia

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Hibernation is of interest to biologists in various fields, but the majority of investigations have been devoted to neurochemical aspects of this phenomenon. Studies of the structural mechanisms providing restructuring of the hibernating organism in critical periods of the year were started in the 60s. Some scientists studied the reactivity of brain structures and endocrine glands of hibernating animals [10,11,13], while others researched the morphological characteristics of a number of organs and systems [5,6,12,14].

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