The Sympathetic Nervous System Is not Involved in the Development of Atropine Tachycardia

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UDC 612.178.2

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny,* Vol. 118, № 9, pp. 234-237, September, 1994
Original article submitted October 25, 1993

There is a consensus that the vagus nerve produces a permanent (tonic) inhibitory effect on heart activity. However, some recent experimental findings attest that the vagus tone is not pronounced and suggest that excitation of the sympathico-adrenal system is the cause of atropine tachycardia. We found in acute and chronic experiments that the blockage of the sympathetic nervous system does not abolish atropine- and methacin-induced tachycardia. At rest heart activity is regulated by the vagus as well as by humoral agents circulating in the blood.

Key Words: *heart; regulation; sympathetic nervous system*

Atropinization and vagotomy of experimental animals are attended by markedly quickened heart contractions [1,3,4,6,10], which the majority of scientists consider to be due to a switching-off of the inhibitory tone of the vagus nerve. Such a conclusion is confirmed by experiments in which pharmacological desympathization [9,11] does not prevent the development of vagotomic tachycardia and decreases the degree of its pronouncement only slightly.

However, there are experimental data [5,7,8] according to which the cause of vagotomic and atropine tachycardia is not the switching-off of the inhibitory tone of the vagus but the excitation of the sympathetic nervous system following deafferentation of the heart or the action of atropine on the central nervous system (CNS) (contradicting the previously accepted opinion on the inhibitory tone of the vagus). In these experiments a significant decrease of vagotomic and atropine tachycardia was noted in dogs after their sympathetic nervous system was switched off by inderal [5].

The sympathetic origin of atropine tachycardia is also proved by the results of experiments [2,5] in which the excitation of the cervical sympathicus in non-narcotized rabbits as a result of intravenous administration of atropine was elecrophysiologically recorded.

The aim of our investigation was to get to the root of the above contradictions and to elucidate the role of the sympathetic and parasympathetic nerves in the regulation of the heart rate (HR).

MATERIALS AND METHODS

Experiments were carried out either at the surgical stage of urethane anesthesia (1.5-2 g/kg i.p. for rats and i.m. for pigeons) or under hexenal anesthesia (70-100 mg/kg i.p. for dogs), or else on alert animals (pigeons and dogs) without anesthesia or any surgical treatment, except for the injection of drugs switching off the autonomic nervous system. M-cholinoreceptors of the parasympathetic nervous system were switched off with atropine or methacin at 0.5-3.0 mg/kg and the sympathetic nervous system was blocked with ornidine (20-30 mg/kg) or inderal (2-3 mg/kg) injected i.p. (rats, dogs) or i.m. (pigeons). In acute experiments the electrocardiogram (ECG), arterial pressure in the common carotid artery, left ventricular pressure, and its first derivative were recorded, while in

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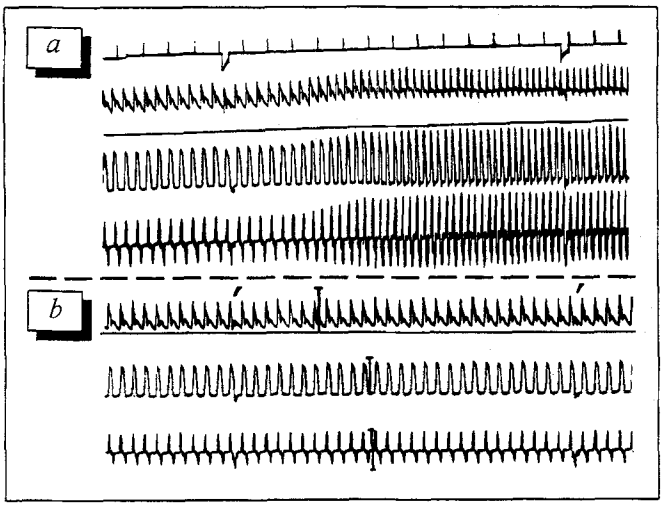

Fig. 1. Changes of cardiac activity in dog for excitation of the stellate ganglion. *a*) before ornidine injection: intensification and quickening; *b*) against the background of ornidine: stimulatory effects are switched off. On each fragment from top to bottom: arterial pressure, left ventricular pressure and its first derivative $\Delta P/\Delta t$. Scale: 25–125 mm Hg, 0–100 mm Hg, respectively, $\Delta P/\Delta t$ 4000 mm/sec.

chronic experiments on alert animals only the ECG was recorded.

During the experiments on the alert pigeons their wings and feet were fixed by a bandage across the body while the head, neck, and tail remained free. The bandaged bird was placed in the natural posture in a cotton "nest." The pigeon was separated from the experimenter by a small screen. Dogs were fixed in a stall with straps near the experimenter. The band of paper was switched on and off noiselessly using a roller device whose motor was continuously running during the experiment, producing a constant soft background noise which lessened the interference from other sounds penetrating the laboratory.

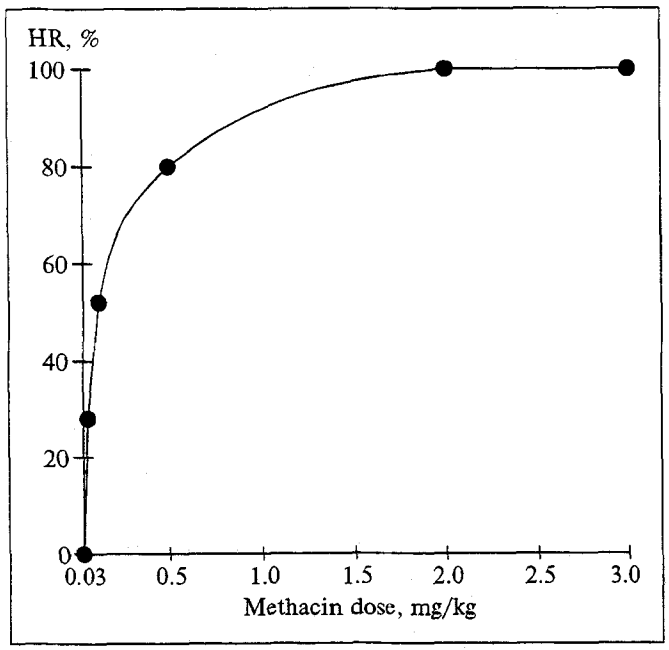

Fig. 2. Increase of the HR in alert pigeons at rest (without anesthesia) following an increase of the methacin dose injected i.m. from 0.03 to 3 mg/kg.

In each experimental series on the alert animals a control ECG recording was performed repeatedly during 20-40 min until the minimal stable level of the HR was reached in an absolutely tranquil experimental animal. Ten to fifteen minutes after the minimal stable HR was recorded, the animal was injected with pharmacological agents blocking the sympathetic or the parasympathetic components of the autonomic nervous system. The HR indexes were recorded 10-15 min after inderal or methacin and 20-30 min after ornidine injection. The time was enough to block the sympathetic and parasympathetic nervous system by these drugs.

RESULTS

Primary evidence of the sympathetic origin of atropine tachycardia [5] is its marked diminishment by sympatholytics, while an incomplete abolishment of atropine tachycardia is considered a result of incomplete blockade of the sympathetic nervous system. In view of this, at the first stage of our experiments on 84 animals of different species (pigeons, rats, dogs) the optimal doses of agents (ornidine, atropine, methacin, and inderal) which reliably block the sympathetic and parasympathetic nervous system were determined according to the absence of an effect during excitation of a nerve. Only then was it possible to obtain convincing evidence of the degree of tone of one or another component of the autonomic nervous system. The stellate ganglion or its cardiac branches were stimulated *in situ* before administration and during the action of ornidine (at 5-30 mg/kg) or inderal (0.5-3.0 mg/kg). For a study of the reliability of vagus blockade the nerve was stimulated in the neck region (its right peripheral part) against the background of atropine or methacin.

It was established that ornidine reliably switches off the sympathetic nervous system only in doses of 20-30 mg/kg (the excitation of the sympathetic nerve under these conditions does not stimulate heart action) (Fig. 1) and that the sufficient dose of inderal is 1-3 mg/kg. A rather strong inhibitory effect was achieved in pigeons by i.m. administration of inderal at 2-3 mg/kg, namely, the excitatory effect on the sympathetic nerve was markedly decreased, but not completely abolished. Subsequently, however, it was confirmed that 2-3 mg/kg is quite sufficient for the blockade of the natural

impulse activity. There is no point in administering inderal at higher doses due to its toxicity.

The parasympathetic inhibitory effect of vagus stimulation was switched off by the M-cholinoblockers atropine and methacin injected in pigeons at 3 mg/kg i.m. and in dogs at 0.5 mg/kg i.p. or s.c. (in the neck region). After the degree of switching-off of the autonomic nervous system by various pharmacological agents in different doses and modes of administration had been studied, the role of the sympathetic system in the development of atropine and methacin tachycardia was directly investigated.

In the first series of these experiments it was found that atropine injections to 11 pigeons and 7 rats resulted in an increase of their HR from 136±5 to 331±13 beats/min (143%, $p<0.001$) and from 273±32 to 392±22 beats/min (44%, $p<0.001$) respectively. The subsequent blockade of the sympathetic nervous system by ornidine lowered the HR in rats only from 392±22 to 372±23 beats/min (5%, $p>0.1$) whereas in pigeons it not only did not lower the HR but actually raised it from 331±13 to 407±12 beats/min (23%, $p<0.001$), which was extremely unexpected and puzzling. These findings attested that in rats the part played by the sympathetic nervous system in the development of atropine tachycardia is a very minor one and the sympathetic tone is not pronounced.

Since by changing the CNS tone anesthesia might affect the autonomic nervous system tone and could thereby result in invalid conclusions, further experiments were performed on alert animals without anesthesia or surgical manipulations except for drug administration. In the first stage the dose of methacin causing the maximal tachycardia was revealed in pigeons (methacin was used due to its stronger effect as compared to atropine and because it does not cross the blood-brain barrier).

The alert animals of this experimental series (Fig. 2) were divided into 4 groups: the 1st group (5 pigeons) received methacin at 0.03 mg/kg; the 2nd group (16 animals) - 0.05-0.1 mg/kg; the 3rd group (11 animals) - 0.5 mg/kg; the 4th group (8 pigeons) - 2.0-3.0 mg/kg i.m. The HR of animals of the 1st group rose from 209±12 to 241±14 beats/min (15%, $p<0.05$); of the 2nd group from 183±8 to 283±30 beats/min (54%, $p<0.02$); of the 3rd group from 172±12 to 308±31 beats/min (79%, $p<0.02$); of the 4th group from 188±13 to 376±19 beats/min (100%, $p<0.001$). The increase of the HR in pigeons was uniformly maximal at methacin doses of 2.0 and 3.0 mg/kg. This means that the effect of the nerve's natural impulse activity is blocked by a lower dose of the preparation than the effect of the impulse activity induced by strong (10-15 V) nerve stimulation.

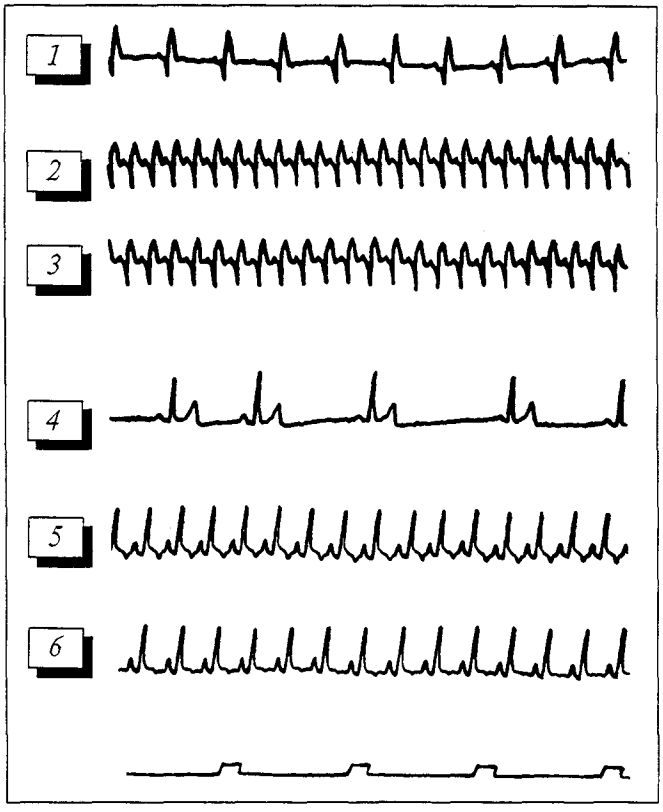

Fig. 3. Changes of the HR in an alert pigeon (*1*, *2*, and *3*) and a dog (*4*, *5*, and *6*) without anesthesia, at rest. *1*, *4*) background; *2*, *5*) after methacin injection (quickening); *3*) after inderal injection (no change); *6*) after ornidine injection (insignificant slowing). ECG recording in all cases; time mark 1 sec.

After these necessary preliminary experiments, we went on to determine the role of the sympathetic nervous system in the development of atropine and methacin tachycardia in alert dogs and pigeons without anesthesia or surgical manipulations. It was found (Fig. 3) that methacin increased the HR in 7 pigeons from 147±9 to 386±33 beats/min (165%, $p<0.001$) and in 9 dogs from 89±6 to 248±11 beats/min (179%, $p<0.001$). The subsequent switching-off of the sympathetic nervous system (by inderal in pigeons and by ornidine in dogs) decreased the HR only to 366±34 beats/min (6%, $p>0.2$) in these pigeons and to 236±14 beats/min (5%, $p>0.1$) in dogs.

In fact, a decrease of the HR related to the abolition of the sympathetic nervous system in dogs, pigeons, and, probably, in rats was absent altogether. Special experiments, performed on 8 pigeons and 9 dogs found that 15-25 min after atropine injection the HR drops by itself without the sympathetic nervous system being switched off (in pigeons by 17 and in dogs by 6 beats/min on average). During an interval of 10-15 min the HR

is more stable. The results of the last two experimental series attested that the tone of the sympathetic nervous system is not pronounced in these animals.

The excitation of the sympathetic nerve registered by some authors [2,5] in an experiment on a rabbit after atropine injection disproves, in our opinion, the sympathetic origin of atropine tachycardia, because in the rabbit the sympathetic nervous system was excited while the HR was not quickened.

Thus, the findings show that the sympathetic nervous system does not participate in the development of atropine tachycardia. The decrease of the HR in experimental animals under anesthesia occurs by itself without the blockade of the sympathetic nervous system. The tone of this autonomic nervous system component is not pronounced either. At rest the HR is regulated by the vagus nerve and humoral substances circulating in the blood.

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