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MECHANISMS OF INHIBITION OF CARDIAC ACTIVITY BY THE STELLATE GANGLION

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It was shown about 50 years ago that stimulation of the stellate ganglion in experimental animals may not only stimulate, but also inhibit the work of the heart [3, 6-9, 11]. The few attempts which have been made to analyze this inhibitory phenomenon, which is unusual for the sympathetic nervous system, have led to contradictory conclusions. For instance, it has been shown [7] that weak stimulation of the sympathetic nerve in rats between the stellate ganglion and the heart reduced, whereas stronger stimulation increased the heart rate. The workers cited concluded that the sympathetic nerve contains cholinergic fibers which inhibit the work of the heart. However, their conclusion was not based on any special investigations, and in addition, the extent of the inhibitory phenomenon (1.5%) in their experiments was within the limits of spontaneous fluctuations of the heart rate [1]. A more penetrating analysis of the mechanisms of this phenomenon showed [11] that stimulation of certain branches given off by the stellate ganglion in cats does not accelerate, but inhibits the work of the heart. Since the inhibitory effect was blocked by hexamethonium and atropine, the authors cited concluded that it is the result of excitation of intracardiac cholinergic neurons, connected synaptically with sympathetic fibers of the stellate ganglion. According to a third hypothesis [4, 5], the inhibitory phenomenon may involve the participation of acetylcholine (ACh) contained in sympathetic endings, which under ordinary conditions facilitates catecholamine (CA) release. Stimulation of sympathetic nerves after exhaustion of CA by reserpine is accompanied by release of ACh by sympathetic endings and the development of a cholinergic effect in various organs, which is abolished by atropine.

Since no general agreement has yet been reached on the mechanisms of inhibition of cardiac activity during stimulation of the sympathetic nerve, these mechanisms were investigated in the experiments described below.

EXPERIMENTAL METHOD

Experiments were carried out on 49 cats weighing 2-3 kg and 28 dogs weighing 5-10 kg. The blood pressure in the left carotid artery, pressure in the left ventricle, and its first derivative ($\Delta P/\Delta t_{max}$) were recorded on a "Mingograf-82" apparatus (Siemens-Elema, Sweden) and N327-5 automatic ink writer, UBP2-03 biopotentials amplifiers, and EMT-35 pressure transducers. The catheter for recording the intracardiac pressure was introduced through the right carotid artery. The animals were anesthetized with hexobarbital or urethane and artificial respiration was applied (apparatus of type 297 and AID-3). Thoracotomy was performed, the sternum was divided by a longitudinal incision, and both vagus nerves were dissected in the neck and divided at the level of the larynx. In acute experiments only the right ganglion, but in chronic experiments both stellate ganglia were dissected in the thorax. To obtain access to them the brachiocephalic artery and the cranial vena cava were ligated and divided. The stellate ganglion was found at the base of the 1st and 2nd ribs and its branches were dissected. Individual branches and the body of the ganglion were stimulated. In cats the cardiac branch (caudal cardiac nerve) was stimulated most frequently, whereas in dogs both branches were stimulated in equal proportions. ÉSL-2 and T-2 stimulators were used (7-15-30-45 V; 20-30 Hz; 1-cm sec, duration 20-30 sec). Different parts and structures of the autonomic nervous system were blocked successively in the experiments either surgically (division of the vagus nerves in acute and chronic experiments, in the latter case the right vagosympathetic bundle was divided to produce degeneration 2-4 weeks before the main part of the experiment),

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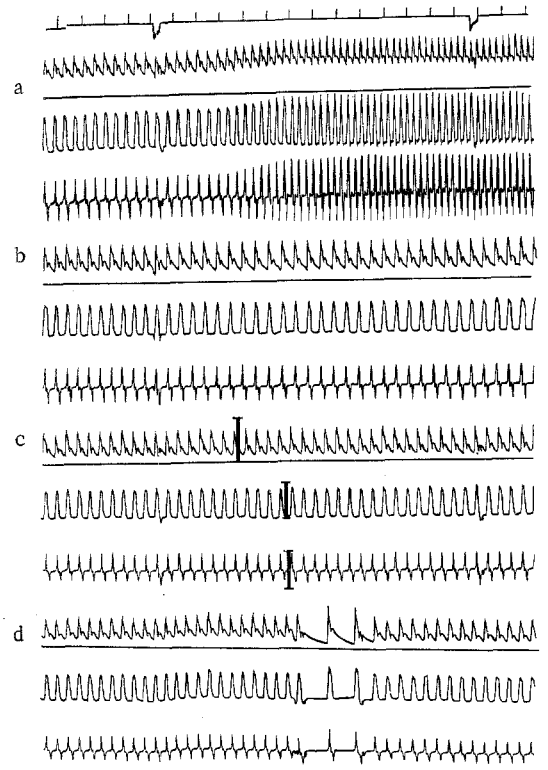

Fig. 1

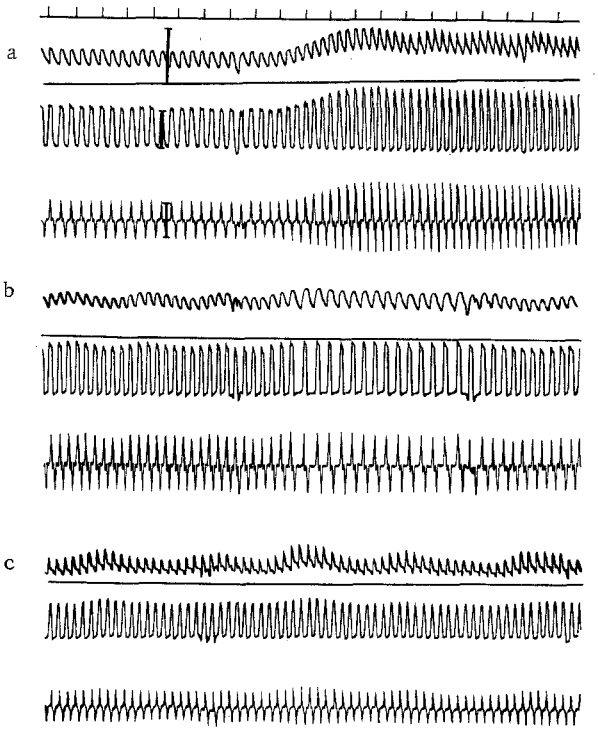

Fig. 2

Fig. 1. Changes in cardiac activity of dog during stimulation of right stellate ganglion under different conditions. a) Before injection of bretylium (acceleration and strengthening); b, c) after bretylium (b — inhibition, c — inhibition not repeated); d) stimulation of right vagus nerve (inhibition). In each fragment, from top to bottom: BP, pressure in left ventricle and its first derivative ($\Delta P/\Delta t$). Scale (from top to bottom): 25-125 and 0-100 mm Hg ($\Delta P/\Delta t$ 4000 mm/sec). Marker of stimulation (arrow) on each fragment of curve, time marker (above) 1 sec.

Fig. 2. Changes in cardiac activity of cat during stimulation of right stellate ganglion. a) Before injection of bretylium (acceleration and strengthening); b) after bretylium (inhibition); c) inhibition blocked by dimecoline. Scale (from top to bottom): 50-150 and 0-100 mm Hg; $\Delta P/\Delta t$ 4000 mm/sec. Time and stimulation marker and order of traces the same as in Fig. 1.

or by the use of drugs: benzohexonium and dimecoline* (2.5-7 mg/kg, intravenously or intraperitoneally), atropine and oxyphenonium bromide (1-2 mg/kg intraperitoneally or 0.2 mg/kg intravenously), bretylium (20-30 mg/kg, intraperitoneally), propranolol (0.5-1.0 mg/kg, intravenously, 2-3 injections), and Rausedil† (1 mg/kg intramuscularly, two injections with an interval of 17-25 h between them at the beginning of the main part of the experiment, followed by addition of propranolol).

EXPERIMENTAL RESULTS

The experiments on dogs showed that stimulation of the right stellate ganglion after division of the vagus nerves but with an intact sympathetic nervous system, caused the usual acceleration (from 184 ± 12 to 261 ± 13, 42%; $P < 0.001$) and strengthening (by 31 ± 2% according to the parameter $\Delta P/\Delta t$; $P < 0.001$) of the cardiac contractions, as well as raising the blood pressure from 103 ± 8 to 127 ± 8 mm Hg (23%; $P < 0.001$). The same procedures after pharmacological blocking of the sympathetic nervous system as a rule caused no change in the work of the heart; this was unexpected, because other workers [11], under similar experimental condi-

*Dimecolonium iodide.
†Reserpine.

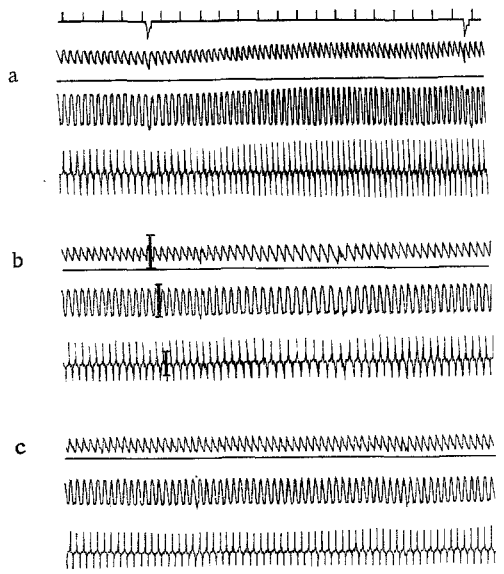

Fig. 3. Changes in cardiac activity of cat during stimulation of right stellate ganglion. a) Before injection of bretylium (acceleration and strengthening): b) after injection of bretylium (inhibition); c) inhibition blocked by oxyphenonium. Remainder of legend as to Fig. 2.

tions, observed inhibition of cardiac activity in cats. To discover the inhibitory phenomenon in this case, parameters of stimulation, anesthesia, and pharmacological agents blocking the sympathetic nervous system were varied over a wide range.

Despite the measures undertaken, inhibition of cardiac activity, which was unstable during repeated stimulation of the stellate ganglion, could be discovered in only three (11%) of the 28 dogs (Fig. 1).

The inhibitory phenomenon developed evidently on account of excitation of parasympathetic fibers of the vagus nerve, which anastomose infrequently in dogs with branches of the stellate ganglion, as is indirectly confirmed by investigations by other workers, who found anastomoses between branches of the cervical sympathetic ganglia and the vagus nerve [2, 10].

Subsequent experiments were performed on cats, because according to data in the literature [11] the inhibitory phenomenon is well defined in these animals.

In the experiments of control series I on 15 cats stimulation of the stellate ganglion before administration of the drugs was found to induce the usual increase in heart rate from 177 ± 9 to 218 ± 11 beats/min (23%; $P < 0.001$) and strengthening of the cardiac contractions by 38 ± 3% ($P < 0.001$ relative to $\Delta P/\Delta t$) and elevation of the blood pressure from 129 ± 8 to 150 ± 8 mm (23%; $P < 0.001$; Fig. 2a). Stimulation of the stellate ganglion after pharmacological blocking of the sympathetic nervous system, however, evoked slowing of the heart rate in 94% of animals from 146 ± 7 to 108 ± 6 beats/min (26%; $P < 0.001$); the blood pressure and force of the cardiac contractions, however, were unchanged (Fig. 2b).

The results of the experiments of series II (11 animals) showed that inhibition of cardiac activity developing in cats during stimulation of the stellate ganglion is effected through preganglionic nerve fibers (the inhibitory effect was blocked by ganglion-blockers), connected synaptically with intracardiac inhibitory neurons (Fig. 2c).

The nature of these neurons was studied in the experiments of series III (11 cats), in each of which stimulation of the stellate ganglion in intact animals was accompanied by acceleration and strengthening of cardiac activity (Fig. 3a), whereas the same procedure after pharmacological blocking of the sympathetic nervous system had an inhibitory effect (Fig. 3b), which was blocked by atropine for oxyphenomium (Fig. 3c), evidence of the cholinergic nature of the inhibitory neurons.

In the experiments of series IV, conducted under chronic conditions on 12 cats after preliminary division and degeneration of the right vagus nerve, stimulation of the right stellate ganglion before administration of the drugs to these animals led as usual to acceleration and strengthening of cardiac contractions. However, the same procedure, after blocking of the sympathetic nervous system, did not induce inhibition of the heart beat in any of the 12 experiments, unlike in all previous experiments on cats, and the same was also true of stimulation of the degenerated right vagus nerve. Meanwhile stimulation of the left stellate ganglion and, naturally, of the left vagus nerve was accompanied by inhibitory effects, which were blocked by ganglion-blockers and atropine.

Inhibition of cardiac activity arising in response to stimulation of the stellage ganglion is thus the result of excitation of parasympathetic fibers of the vagus nerve, anastomosing with branches of the stellate ganglia and running in their composition to the heart.

The hypothesis that preganglionic sympathetic nerve fibers relay to intracardiac cholinergic neurons [11] and also the hypothesis of a chloinergic component in sympathetic endings [4, 5] were not confirmed. In experiments by the authors cited the cholinergic effect of stimulation of sympathetic nerves against the background of adrenolytics develops because they stimulated mixed nerves, containing sympathetic and parasympathetic nerve fibers. Consequently, Dale's well known principle that one neuron exerts its efferent influence by means of one mediator, remains valid. The results of the present experiments also demonstrate that α-adrenoreceptors have no marked effect on cardiac activity.

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