PHYSIOLOGY

Tone of Sympathetic Nerves and Regulation of Heart Activity

V. M. Smirnov

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Tone of sympathetic nerves to the heart was studied in rats and guinea pigs. Experiments with pharmacological blockade of the sympathetic nervous system and vagotomy confirmed the general notion on the absence of tonic effects of sympathetic nerves on the heart. Reduction of the heart rate reported previously probably attests to various experimental designs (type and depth of anesthesia, possible hypothermia, duration of observations, and pharmacological preparations). As differentiated from the vascular tone, the heart rate under rest conditions depends on the vagal tone and circulating humoral substances.

Key Words: *heart; sympathetic nerve; tone; regulation*

Tone of autonomic nerves plays an important role in adaptive reactions of the body. Its variations are accompanied by inhibition or stimulation of functions of various organs. In particular, increased tone of the sympathetic nerves (SN) leads to acceleration, while decreased SN tone is associated with reduction of the heart rate (HR). However, the presence and degree of the tone of the sympathetic nervous system (SNS) to the heart remain unclear [5].

It is believed that unlike pronounced tone of the vagus nerve (VN), tone of SN is low or even absent [1,2]. This is confirmed by the fact that inhibition of SNS with reserpine or propranolol only slightly attenuates atropine- and vagotomy-induced tachycardia in dogs and cats [7,9]. Propranolol-induced inhibition of SNS in intact dogs and humans produces no effect [11] or slightly decreases HR [8].

However, there are contradictory notions that the tone of SN to the heart is high. It was reported that blockade of SNS in dogs reduces HR from 100 to 60 bpm (by 40%) [4]. However, under rest conditions vagal tone is higher than tone of SN, because HR in denervated heart surpasses that of the intact organ [4]. Experiments on dogs also showed that propranolol (β-adrenoceptor blocker) reduces HR by 25% [13].

The presence of SNS tone was demonstrated in experiments on narcotized crucian carps at 20-25°C. β-Adrenoceptor blockade with 1 mg/kg propranolol decreases HR by 22% [6]. Fluorescence assay revealed adrenergic innervation in all heart chambers of crucian carps [6]. Some authors believe that SN tone is most pronounced in rabbits, rats, and hens [10].

The presence of SN tone is also confirmed by human observations. Blockade of the right stellate ganglion in 17 individuals reduces HR from 80 to 69 bpm, while blockade of the left stellate ganglion causes no bradycardia [12].

Here we studied SN tone and its role in the regulation of heart activity.

MATERIALS AND METHODS

Particular attention was given to experimental conditions (doses of pharmacological preparations, type of anesthesia, duration of observations, and possible hypothermia) to eliminate instrumental errors [3].

Experiments were performed on 41 outbred rats, 29 guinea pigs, and 8 pigeons during the surgical stage

Department of Physiology, Russian State Medical University. ***Address for correspondence:*** vms@doctor.com. Smirnov V. M.

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of urethane anesthesia (1.5-2 g/kg intraperitoneally). SNS was inhibited with intraperitoneal bretylium tosilate (BT, 30 mg/kg). Electrocardiogram was recorded in standard lead II. HR parameters were measured 20-30 min after injection of SNS inhibitor. SNS was considered to be blocked if stimulation of SN produced no changes in HR. The chest was opened and the animals were artificially ventilated. Both VN were prepared on the neck, and laryngeal vagotomy was performed. The right stellate ganglion localized in the thoracic cavity was prepared. In rats and guinea pigs, the brachiocephalic artery and vena cava were ligated and transected. We prepared branches of the stellate ganglion lying near the proximal tips of ribs I and II. Accelerator nerves in birds arise from the 1st thoracic sympathetic ganglion and give individual coronary branches forming plexuses with VN. Feathers were pulled out, the skin was dissected along the lateral and lower margins of the right scapula, and muscles between the scapula and ribs were exfoliated. The scapula was swung with a ligature fixed to its lower margin (40-60° to the body axis), and rib III was excised. The accelerator nerve was localized under rib II. Cervical VN were prepared and transected; the muscle tissue remained intact.

RESULTS

In series I performed on 10 rats and 12 guinea pigs, the doses of pharmacological preparations inhibiting SNS were determined. The stellate ganglion or its coronary branches were stimulated before and after injection of 5-30 mg/kg BT (the dose was so adjusted that nerve stimulation did not change heart activity).

BT blocked SNS activity only in a dose of 20-30 mg/kg. In the next series, we studied the tone of SNS.

Series II was performed on 16 unoperated rats narcotized with urethane (surgical stage). SNS blockade with 30 mg/kg BT did not reduce HR, and even slightly increased it from 309±16 to 327±17 bpm (by 6%, insignificant, Fig. 1, *1*, *2*). If SN to the heart have a pronounced tone, their blockade should decrease, but not increase HR.

In series III, we stimulated VN in 7 rats, 7 guinea pigs, and 8 pigeons. BT suppressed VN activity in pigeons (similarly to the effect on SN) and, therefore, elevated HR. In rats and guinea pigs, the inhibitory effect was not attenuated after BT administration (at least, during stimulation of VN). However, it cannot be excluded that under natural conditions BT slightly attenuates the inhibitory effect of VN on heart activity. This probably accounts for insignificant elevation of HR after partial suppression of vagal inhibitory effects.

To evaluate the role of SN tone in the regulation of heart activity, series IV was performed on 10 guinea pigs under urethane anesthesia. SNS blockade with 30 mg/kg BT did not change HR in these animals (317±8 *vs.* 315±7 bpm in the control, $p>0.05$, Fig. 1, *3*, *4*).

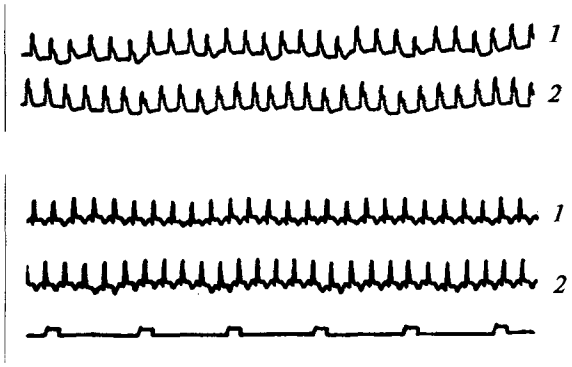

Fig. 1. HR in rats (*1*, *2*) and guinea pigs (*3*, *4*) during surgical stage of urethane anesthesia: before (*1*, *3*) and after BT injection (no changes, *2*, *4*). ECG. Bottom: time mark=1 sec.

Thus, experiments on guinea pigs and rats confirm the general notion on the role of SN tone in the regulation of heart activity.

It is believed that SNS tone is most pronounced in rats [10]. However, in our experiments inhibition of SNS activity under conditions of intact VN did not reduce HR, which indicated the absence of SN tone to the heart.

Since activity of intact parasympathetic nervous system could introduce errors in the measurements, series V was performed on 8 rats with transected VN. In this case, HR variations after BT administration result only from the inhibition of SNS activity. Vagotomy elevated HR from 338±19 to 469±11 bpm (by 39%, $p<0.001$, Fig. 2, *2*), which indicated pronounced inhibitory effects of VN in rats. SNS suppression with 30 mg/kg BT decreased HR in vagotomized animals from 469±11 to 449±19 bpm (only by 5%, $p>0.1$), which also indicated the absence of SNS tone in rats (Fig. 2, *3*).

Experiments on vagotomized rats showed that the elevation of HR after BT administration to animals

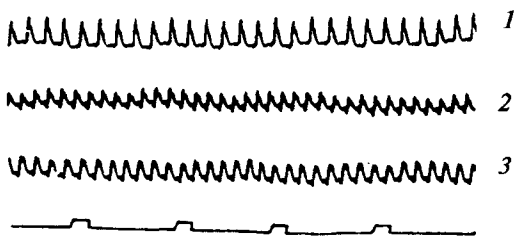

Fig. 2. HR in rats: after preparation of the vagus nerves and before injection of pharmacological preparations (*1*); after bilateral vagotomy, tachycardia (*2*); after BT injection (blocker of the sympathetic nervous system), no changes (*3*). ECG. Bottom: time mark=1 sec.

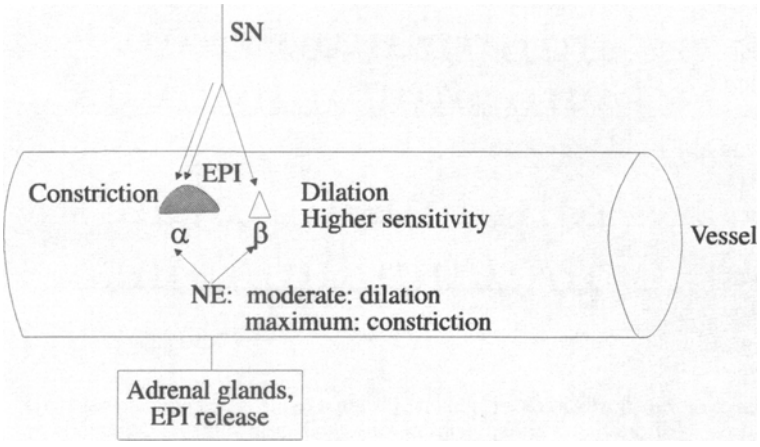

Fig. 3. Adrenergic regulation of vascular tone. SN: sympathetic nerve; a and b: α- and β-adrenoceptors; EPI: epinephrine; NE: norepinephrine; arrow: activation; double arrow: pronounced activation of adrenoceptors. α-Adrenoceptors are shown by large symbols, because their density in vessels is higher than that of β-adrenoceptors. Simultaneous activation of α- and β-adrenoceptors leads to vasoconstriction.

with intact VN resulted from partial suppression of their inhibitory effects.

Our experiments showed that marked reduction (by 20-40%) of HR in dogs and fishes reported previously is determined by experimental designs (anesthesia, surgery, and possible hypothermia), rather than inhibition of SNS. During the surgical stage of hexenal and nembutal anesthesia we observed not only the blockade of nociceptive and other reactions of the body to surgery, but also inhibition of the vagal tone [3]. Vagotomy or atropine administration to experimental animals caused no tachycardia. At the same time, these procedures performed under urethane anesthesia led to pronounced tachycardia in pigeons and dogs and, to a lesser extent, in rats. If SNS activity was blocked after vagotomy or atropine injection, tachycardia gradually decreases without sympatholytic administration [3].

Hence, the tone of SN to the heart in animals at rest is absent, which is consistent with published data [2,4].

It should be emphasized that the tone of SN to vessels is relatively high. Therefore, α-adrenoceptor blockade causes dilatation of blood vessels and reduces blood pressure. By contrast, stimulation of SNS (*e.g.*, during emotional stress) elevates blood pressure via increasing the rate and strength of cardiac contractions. This primarily results from vasodilation and activation of β-, but not α-adrenoceptors. These changes are accompanied by activation of vascular α- and β-adrenoceptors [4]. It is known that activation of α-adrenoceptors leads to vascular smooth muscle contraction and vasoconstriction. By contrast, activation of β-adrenoceptors is accompanied by vasodilation. α-Adrenoceptors in vessels are more abundant than β-adrenoceptors and, therefore, vasoconstriction predominates (Fig. 3). It should be emphasized that small coronary vessels contain mainly β-adrenoceptors. Therefore, activation of the sympathoadrenal system causes dilation of small coronary vessels; by contrast, large coronary vessels having a considerable number of α-adrenoceptors are constricted (similarly to vessels in other organs). In this case, blood supply to the heart often remains unchanged. The release of epinephrine from the adrenal glands is probably the mechanism protecting the heart and other organs during emotional stress. Epinephrine activates both α- and β-adrenoceptors, but β-adrenoceptors are more sensitive than α-adrenoceptors. Therefore, the increase in blood epinephrine concentration leads to vasodilation in the heart and other organs. This is confirmed by skin redness and warm sensation due to dilation of skin vessels.

However, severe emotional stresses are accompanied by massive release of epinephrine, which leads to activation of not only β-, but also α-adrenoceptors. This causes vasoconstriction in all organs. The face becomes pale, and subjects feel cold due to constriction of skin vessels. Small coronary vessels are dilated, although blood supply to the heart remains unchanged or even decreases due to constriction of large coronary vessels mainly containing α-adrenoceptors. In any case, the predominance of β-adrenoceptors in small coronary vessels serves as a protective factor.

At rest, SNS does not change the strength and rhythm of cardiac contractions due to the absence of tonic effects on the heart. In this case, heart activity is determined by vagal tone and circulating humoral substances. Intensification of heart activity during physical exercises or emotional stress is related to suppression of vagal inhibitory effects, activation of the sympathoadrenal system, and the release of biologically active substances (mainly catecholamines) into the circulation.

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