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A CENTRAL NORADRENERGIC MECHANISM RESPONSIBLE FOR MODULATION OF THE ARTERIAL BARORECEPTOR REFLEX IN CATS

V. S. EREMEEV, Ph.D.
R. S. KHRUSTALEVA, Ph.D.
V. A. TSYRLIN, Ph.D.
Yu. I. SHCHERBIN, Ph.D.

THE DEPARTMENT OF EXPERIMENTAL AND CLINICAL PHARMACOLOGY
RESEARCH INSTITUTE OF CARDIOLOGY
15 PARKHOMENKO PR.
ST. PETERSBURG, 194156, RUSSIA

Valery S. Eremeev received his Ph.D. from the First Medical Institure of Leningrad in 1968. He is currently retired. Raisa S. Khrustaleva received a Ph.D. from the State University of Saint-Petersburg in 1994. Vitaly A. Tsyrlin receied a Ph.D. from the First Medical Institute of Leningrad in 1967. He is currently Professor and Head of the Departament of Experimental and Clinical Pharmacolodgy of the Research Institute of Cardiology. Yuri I. Shcherbin received a Ph.D. from the State University of Saint-Petersburg in 1992. At present, the three of them are working at the Departament of Experimental and Clinical Pharmacolodgy of the Research Institute of Cardiology, Saint-Petersburg, Russia.

Dr. Khrustaleva can be reached at 7-(812) 550-07-00. Dr. Tsyrlin can be reached at 7-(812) 244-29-61 or via email at tsyrline@ric.spb.su. Dr. Shcherbin can be reached at 7-(812) 550-07-00 or via email at yui@ric.spb.su.

Introduction

It has been shown that in anaesthetized and conscious animals norepinephrine administrated intravenously for a long time produces a sustained inhibition of the renal nerve sympathetic activity (3, 4, 6, 8). This effect is mediated by an enhanced action of the central limb of arterial baroreceptor reflex (2, 4). At least two neural mechanisms

are responsible for modulation of the baroreflex response by norepinephrine: brainstem neurons are excited or suppressed by norepinephrine and a reflex involving spinal afferent pathways.

An increase in arterial pressure over norepinephrine infusion may be a factor that contributes in damage to the blood-brain barrier. In that circumstances norepinephrine enters the brain and directly excites adrenergic receptors in central nervous system. On the other hand, systemic infusion changes tissue energic metabolism and so stimulates peripheral receptors in many organs. This effect results in an increase of afferent traffing in spinal nerves. In turn, the afferent activity can affect the size of the arterial baroreflex (7).

Proceeding from the above, the purpose of this study is to find a mechanism responsible for augmentation of the arterial baroreflex following intravenous infusion of norepinephrine.

Methods

In total, 18 experiments were performed on anaesthetized (alpha chloralose), immobilized, and artificially ventilated cats. Arterial pressure was monitored with a catheter positioned via the femoral artery in the aorta and connected to a pressure transducer (746 Siemens-Elema AB, Sweden). The left renal and inferior cardiac nerves were separated from the surrounding tissue, cut distally, and covered with warm mineral oil for subsequent recording of action potential from the central cut end of the nerve. Platinum hook bipolar electrodes were used to record nerve traffic. The sympathetic nerve activity was amplified by a preamplifier filtered between 10 and 3000 Hz. The whole nerve activity was obtained by rectifying and integrating the action potentials with a cumulative integrator (resetting every 1 s). In all experiments, the sinus nerves and the vago-sympathetic trunks were sectioned bilaterally. The central end of the left sinus nerve was placed on platinum hook bipolar electrodes for subsequent stimulation and covered with mineral oil.

Norepinephrine and angiotensin II were administrated intravenously for one hour. In each experiment the infusion rate of the substances was selected individually to ensure the initial elevation of mean arterial pressure by 40-60 mm Hg. The sinus nerve was stimulated by square pulses (40 Hz, 0.5 ms, 0.5-8 V) continuously for 1 min before infusion, at the 10-th, 30-th, 60-th min of infusion, and at the 10-th, 30-th, 60-th min after the infusion was stopped. The suppression of sympathetic nerve activity during any continuous stimulation of the sinus nerve was evaluated as a ratio of integral activity over the stimulation to activity for the same time (1 min) before the stimulation.

The experiments were performed in three series. The first experiments (6 cats) were carried out to determine an increase of the renal nerve activity suppresson induced by electrical stimulation of sinus nerve under the action of norepinephrine infusion. In the second series (7 animals) sympathetic activity was recorded in the inferior cardiac nerve. To interrupt afferent impulses to brain we sectioned the spinal cord at the 4-5 thoracic segments and the nerves of the both brachial plexus going to the forelimbs. Repetitive stimulations of the sinus nerve and norepinephrine infusion were done two times - before and after the central nervous system was partly deafferented. In the final group of experiments we infused angiotensin II and recorded sympathetic activity from renal nerve. The sinus nerve stimulation was performed as in the first group of experiments. The alpha-adrenergic receptor blocker phentolamine (2.0 mg/kg) was administered into the vertebral artery at the 55-th min of the infusion.

We used infusion of angiotensin II for two reasons. The first reason was to avoid a large decrease in arterial pressure after an injection of phentolamine. Secondly, thanks to the fact that angiotensin II has the ability to release norepinephrine from axon endings (1), we could find an involvement of central noradrenergic mechanisms in the baroreceptor reflex modulation.

For mean arterial pressure and renal nerve integral activity channels, the analog outputs from special devices were connecteed to a paper recorder and to an analog-to-digital converter. Data were acquired, stored, and analyzed using a PC-AT computer. Mean arterial pressure and renal nerve integral activity were sampled at frequency of 1 Hz.

The statistical graphics system STATGRAPHICS was used to analyse the data. For the comparison of means the Student's t-test was applied. Differences were considered to be significant for $p < 0.05$. The results are presented as means +/- SE.

Results

In the first series of experiments a control sinus nerve stimulation evoked depression of renal nerve activity by 87+/-8 %. The norepinephrine infusion increased blood pressure by 56+/-4 mmHg but the infusion did not change ongoing renal nerve activity. At the 10-th min of the infusion the sinus nerve stimulation of the same value evoked suppression of renal nerve activity by 49+/-7 % ($p<0.01$). At the 60-th min of the infusion the sinus nerve stimulation induced the nerve activity depression by 24+/-5 % ($p<0.001$). The depression of nerve activity due to the sinus nerve stimulation returned to the control value at the 60-th min after the infusion was stopped (Fig. 1).

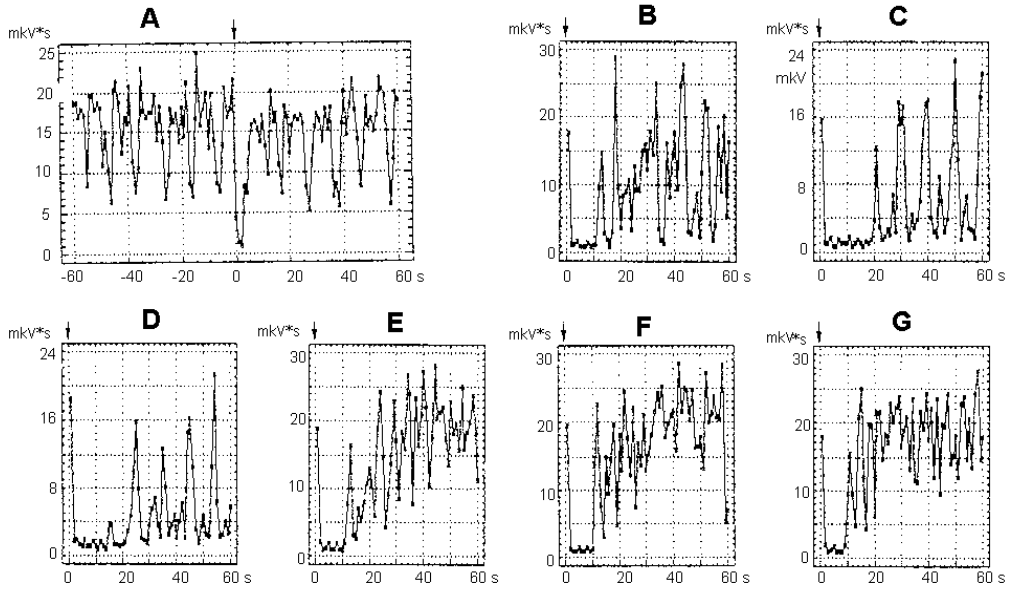

Figure 1. The inhibition of the renal nerve electrical activity evoked by stimulation of the sinus nerve over 60 s with norepinephrine infusion in the cat (one experiment). A - the control stimulaton; B - the 10-th min of the infusion; C - the 30-th min of the infusion; D - the 60-th min of the infusion; E - 10 min after the infusion; 30 min after

the infusion; 60 min after the infusion. The arrow indicates the beginning of the stimulation.

This effect of norepinephrine infusion on the suppression of the cardiac nerve activity due to the sinus nerve stimulation was preserved after the spinal cord and some nerves of both brachial plexus were severed.

In the third series of experiments the infusion of angiotensine II resulted in an increase of suppression of the renal nerve activity evoked by the sinus nerve stimulation. At the end of the infusion the suppression of the nerve activity was larger than the suppression of nerve activity in the beginning of the infusion. Phentolamine injection removed the increase of the suppression of renal nerve activity evoked by electrical stimulation of sinus nerve during infusion of angiotensin II (Fig. 2).

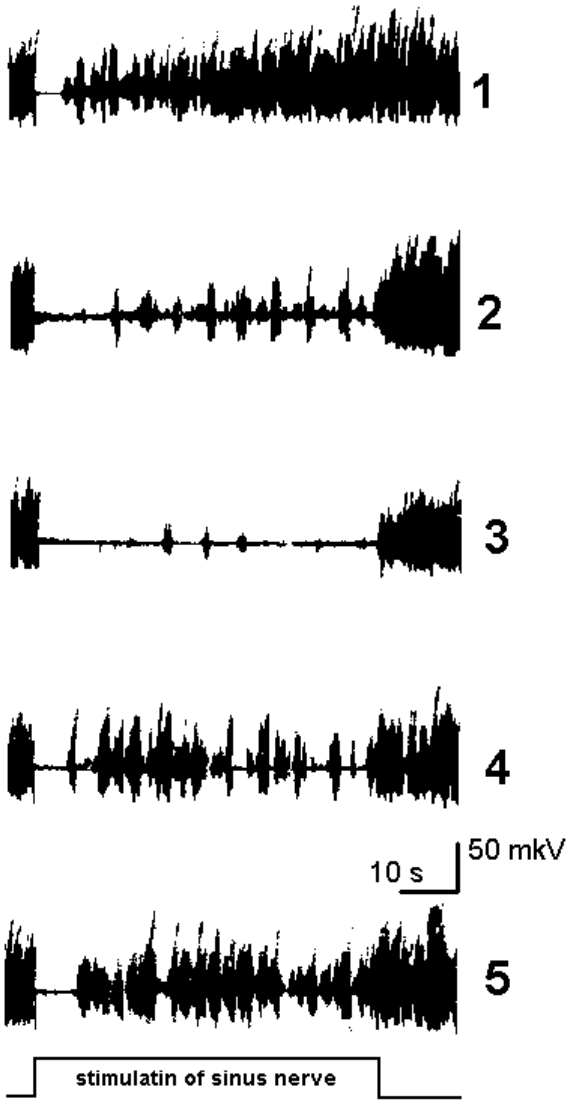

Figure 2. Changes in intensity of the inhibition of electric activity of the renal nerve evoked stimulation of the sinus nerve during angiotensin II infusion and phentolamine administration into the vertebral artery (one experiment; an original record). Fragments of recording: 1 - control; 2 - the 10-th min of A II infusion; 3 - the 30-th min of A II infusion; 4 - 30 sec after the administration of phentolamine into the vertebral artery; 5 - 5 min after the administration of phentolamine during A II infusion.

Discussion

It has been shown formerly that the sympathetic activity escapes from the inhibitory influences of baroreceptor afferents (5). This fact was reproduced in our experiments. The duration of the sinus nerve stimulation was 60 s but the renal nerve discharges were inhibited during 10 s only (fig. 1A). The duration of the inhibition increased under the action of norepinephrine and the increased inhibition was preserved for some time after the norepinephrine infusion was stopped. Perhaps owing to this in experiments on animals with an intact baroreceptor reflex the sympathetic activity was depressed after the infusion even if arterial pressure was restored (4, 6). To determine the role of interoreceptors in the modulation of baroreceproor reflex we tryed to remove as many as possible afferent impulses from organs and tissues to brain. The inhibition of the inferior cardiac nerve activity elisited by sinus nerve stimulation over the norepinephrine infusion before and after the denervation of the central nervous system was compeared. The results of that experiments indicated that in this case the afferent impulses from interoreceptors did not contribute to enhanced action of the central limb of arterial baroreceptor reflex.

Proceeding from the above, entry of norepinephrine from blood into brain and modulation of synaptic excitability in certain neuron populations appears to be the cause of the increase in the baroreflex inhibition of sympathetic activity. The administration of phentolamine into the vertebral artety blocked the adrenomimetic action of angiotensin II. As shown in fig. 2, the effectiveness of the sinus nerve stimulation after phentolamine was like that before the infusion of angiotensine II.

Thus, the data obtained corroborate the supposition that norepinephrine administrated intravenously can modulate the activity of the arterial baroreceptor reflex in its central limb. In this way norepinephrine and angiotensine II can block escape of sympathetic activity from inhibitory influence of buffer nerves. Perhaps, the obtained effect of exogenous norepinephrine and angiotensine II is not a laboratory phenomenon. The increase of baroreceptor reflex may occur with stress and pheochromocytoma and act against the extremely large vasoconsrictor nerve activity for a long time.

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