PHYSIOLOGY

Role of Chemoreceptors in the Zone of Vertebral Arteries in the Formation of the Cardiorespiratory Functional System

N. A. Agadjanyin and S. V. Kupriyanov

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Chemoreceptors in reflexogenic zones of the vertebral and carotid arteries play a regulatory role in the cardiorespiratory interaction. Perfusion of these zones with lactic acid solution (0.5-3.0 mmol/liter) produced a reflex response, which was manifested in stimulation of external respiration and increase in systemic blood pressure. The reflex response of these systems was opposite after local administration of 0.3 M Tris-buffer. Correlation analysis revealed the role of afferentation from reflexogenic zones in the formation of a regulatory functional system for tissue gas exchange and acid-base balance.

Key Words: *vascular reflexogenic zone; vertebral artery; carotid sinus; cardiorespiratory system*

Various groups of interoceptors (mechanoreceptors, chemoreceptors, thermoreceptors, and osmoreceptors) are present in all organs and tissues. Stimulation of these receptors causes a variety of reflex responses. The majority of these responses have an important regulatory role. The vascular reflexogenic zone (VRZ) is one of the receptor structures. Functions of the sinocarotid and aortic VRZ were studied in details [8-10]. They received the name "standard zones". Little attention is paid to the search and study of previously unknown VRZ. For example, there are no data on the regulatory role of chemoreceptors in the vertebral artery zone (VAZ). Clinical observations provide indirect evidence for baroreceptor activity of the vertebral arteries [6,11,12]. They play the major role in the supply of nutrient substances to the base of the brain. The role of VRZ chemoreceptors in the formation and regulation of cardiorespiratory functional systemic reactions remains unknown.

Department of Normal Physiology, I. N. Ul'yanov Chuvash State University, Cheboksary, Russia. ***Address for correspondence:*** kuper_sv@yandex.ru. S. V. Kupriyanov

Our previous studies revealed the proper and combined baroreflex and chemoreflex influences of VAZ on systemic blood pressure (SBP), electrical activity of the heart, vascular tone in skeletal muscles and internal organs, capacitance properties of blood pool in the spleen, arterial tone of the bulbar conjunctiva, retina, and inner ear, and external respiration. Moreover, they play a system-organizing role in the regulation of tissue gas exchange [4,5].

Here we compared the chemoreflexes from hemodynamically isolated vertebral arteries (with intact nervous pathways) and standard sinocarotid zone.

MATERIALS AND METHODS

Experiments were performed on 54 adult male and female cats (2.0-4.3 kg) under urethane anesthesia (1 g/kg) and natural ventilation. The baseline blood pressure was 100-130 mm Hg. External respiration was recorded using the Marey's capsule with modifications. SBP in the femoral artery was measured by the occlusion method. The linear data input of external

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respiration and SBP was performed using two electromanometers (MEP-I-01) and electronic attachments.

VAZ and carotid artery zone were isolated hemodynamically as described elsewhere [2]. The carotid sinus was routinely isolated. In some series, the aortic zone was pharmacologically denervated.

Acidotic stimulation of VRZ was performed with D,L-lactic acid (2-hydroxypropionic acid, $C_3H_6O_3$; 0.5-3.0 mmol/liter) in physiological saline. The minimum concentrations (pH 7.34-7.08) correspond to a normal and elevated content of lactate (natural metabolite) in blood plasma [1]. Experimental alkalosis was induced by administration of 0.3 M trisamine solution (Tris-aminomethane or Tris-buffer; used in medical practice) into VAZ. Chemoreceptors of these zones were stimulated by constant-pressure perfusion (110±20 mm Hg) of the corresponding arteries. This treatment was not accompanied by activation of baroreceptors.

The results were analyzed by means of Excel software (Statistica). The significance of differences was evaluated by Student's *t* test and rank test.

RESULTS

A total of 101 sessions were performed with lactic acid solution. Comparative analysis was conducted with randomly selected samples, which suggested alternative administration of lactate into the hemodynamically isolated VAZ (n=34) and zone of the carotid sinus (n=20). This treatment produced the same reflex response, which was manifested in stimulation of external respiration and increase in SBP (Fig. 1, *I*). The reflex responses in VRZ of the carotid arteries were more pronounced under these conditions (p<0.01).

Administration of trisamine buffer solution into these zones (40 sessions with VAZ and 22 sessions with the carotid artery zone) was followed by a reflex inhibition of the cardiorespiratory system (p<0.05). These changes manifested in a decrease in the amplitude and rate of external respiration and reduction of blood pressure in the main arteries (Fig. 1, *II*; Fig. 2, *a*).

The following data show a reflex type and chemical nature of these reactions. First, directionality of the reflex influences on the respiratory and cardiovascular system did not depend on lactic acid concentration in the perfusate. Quantitative analysis of these reactions showed that the degree of reflex responses is directly proportional to the concentration of a solution. For example, variations in external respiration and SBP were more pronounced after treatment with lactic acid in a concentration of 3.0 mmol/liter (compared to experiments with 0.5 mmol/liter lactic acid; Table 1). These results illustrate the law of force interactions, which is typical of functional activity of CNS nuclei. Second, all parameters returned to or approached the normal value after termination of chemoreceptor activation in VAZ or carotid artery zone. Third, any reflex response consists of the following stages: short latency (several seconds); maximum response; and aftereffect. The above mentioned stages were revealed in our experiments. And fourth, these reactions were repeatedly observed in the same series. Moreover, the reflex influence of these zones was not reproduced during perfusion with physiological saline. It was associated with the absence of afferentation from baroreceptors under these conditions of stimulation.

In physiology, the main evidence for the reflex type of the reaction is the absence of this reaction after Novocain blockade of the corresponding receptive field. In our experiments, all reactions disappeared 15-

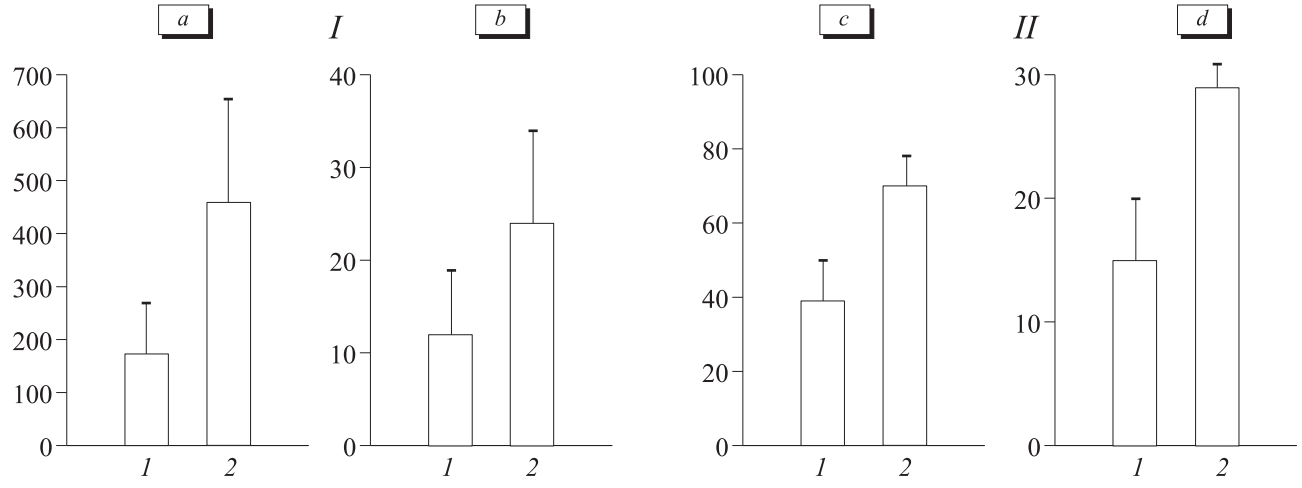

Fig. 1. Comparative analysis of reflex responses in VAZ and carotid artery zone. *I*, activation with lactic acid solutions (0.5-3.0 mmol/liter); *II*, trisamine solution, 0.3 M. (*a*) Variations in external respiration, percent of the baseline value (ΔRMV); (*b*) variations in SBP (Δp, mm Hg). Reflexes from VAZ (*1*) and zone of the carotid sinus (*2*).

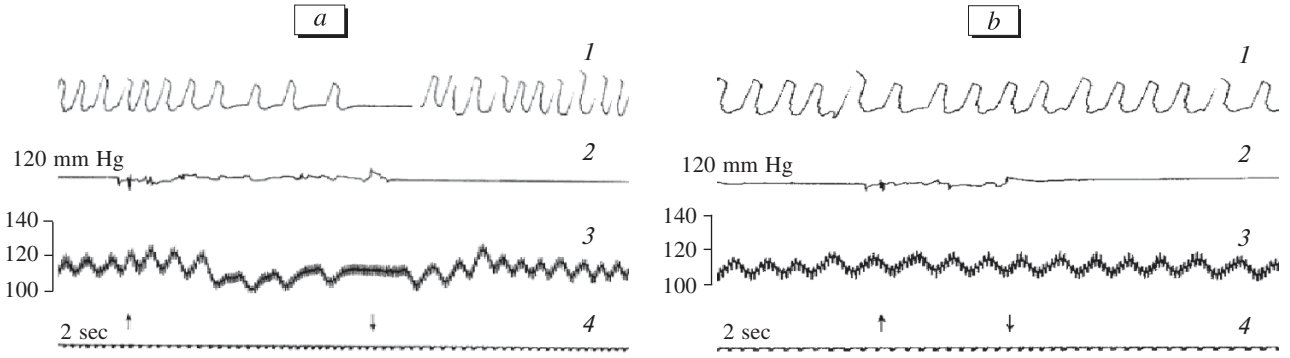

Fig. 2. Inhibition of the cardiorespiratory response (*a*) during vertebral artery perfusion with trisamine solution and after Novocain blockade of VAZ (*b*). Pneumogram (*1*); local pressure in the humorally isolated VAZ (with the isoline, 120 mm Hg, *2*); SBP and calibration (*3*); start (↑) and end of treatment (↓, *4*). Duration of treatment: 52-53 sec (*a*); 10 sec (*b*).

20 min after administration of 2% Novocain solution to vascular zones (Fig. 2, *b*).

Similarly to the carotid sinus, chemoreceptive and baroreceptive properties of VAZ contribute to the reflex regulation of SBP and external respiration. This regulation also involves the cardiovascular and respiratory centers. For example, the development of acidosis is accompanied by an initial increase in functional activity of VRZ chemoreceptors. These changes are directed toward an increase in pulmonary ventilation and oxygenation of the blood. Simultaneous increase in SBP provides supply of hyperaerated blood to tissues. The recovery of gas exchange in tissues is followed by an increase in activity of VAZ baroreceptors [3]. This reaction contributes to a decrease in the elevated blood pressure, which returns to normal in the follow-up period. This interaction between the respiratory and cardiovascular centers probably determines the homeostasis of gas exchange and acid-base balance in peripheral regions. The opposite, but functionally similar changes in cardiorespiratory relationships are realized during an initial increase in blood pH (trisamine treatment in our experiments).

Functional and systemic association of the reactions in various anatomical systems can be proven by correlation analysis [7]. The results of 50 sessions were analyzed by the Pearson test to reveal a correlation between variations in external respiration and SBP. The correlation coefficient (q) was +0.65. These data illustrate the existence of a direct moderate-to-strong correlation between test parameters. Our findings confirm the existence of a coordination mechanism for the reactions of the respiratory and cardiovascular centers to afferentation from VRZ. Therefore, the observed reflex responses are of a systemic and functional type. This conclusion is confirmed by another study to calculate the Hildebrandt index. This index characterizes the intersystemic relations between respiration and

TABLE 1. Qualitative and Quantitative Analysis of Reflex Changes in External Respiration and SBP during Perfusion of VAZ with Lactic Acid Solutions ($M\pm m$)

Concentration of solutions, mmol/liter	Before Novocain treatment					After blockade	
	baseline SBP, mm Hg ($p<0.01$)	variations in blood pressure		depth of external respiration	significance (rank test)	*n*	no response, *n*
		increase		stimulation			
		n	mean value, mm Hg ($p<0.01$)	mean value (percent of the initial level; $p<0.01$)			
0.5-1.0, ***n***=26	117.26±3.32 v=0.084	19	11.73±1.21	133.33±67.39	<0.05	4	4
1.0-2.0, ***n***=46		35	19.00±2.84	174.75±83.85	<0.01	12	12
2.5-3.0, ***n***=9		8	35.49±6.20	230.28±102.85	<0.05	1	1
Total 81*		62				17	17

Note. Baseline parameters of external respiration are taken as 100%. v, relative standard deviation. *Total number of observations during acidotic activation of VAZ (without control values). Significance relative to the baseline (pretreatment) value.

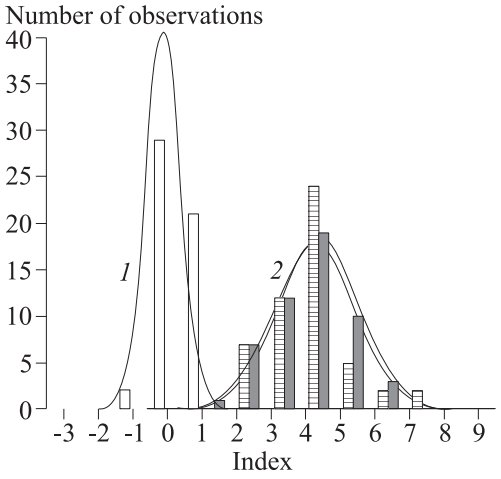

Fig. 3. Histograms of distribution probability density for variations in the Hildebrandt index during afferentation from VRZ of the vertebral and carotid arteries (relative to the baseline value). Significance of variations in test parameter (Q_1-Q_0, *1*); absolute value of the Hildebrandt index before (Q_0) and after (Q_1) activation of VAZ or carotid artery zone. Abscissa: Hildebrandt index. Ordinate: number of observations. Light bars, Q_1-Q_0 -0.13±0.51; dark bars, Q_1 4.23±1.12; shaded bars, Q_0 4.37±0.12.

hemodynamics. In healthy people, the Hildebrandt index is 2.8-4.9. The Hildebrandt index under resting conditions (before activation of receptors in VAZ and carotid artery zone) was 3.25-5.6 (δ=0.14). Cardiorespiratory interactions were not impaired during the realization of reflex responses (in spite of variations in frequency characteristics of respiratory and cardiac functions; Fig. 3). The Hildebrandt index remained practically unchanged and did not differ from the baseline (pretreatment) value.

We conclude that the vertebral arteries include a separate reflexogenic zone, which is functionally similar to the standard VRZ in the carotid sinus. Their combined chemoreceptive activity is directed toward the regulation of external respiration and SBP. After variations in baseline pH of the blood, they are integrated into the joint cardiorespiratory functional system. Motivation of the functional system is realized via afferentation from VRZ. Functional activity of this system is manifested in the described chemoreflexes. Reflex influences of VAZ and carotid sinus provide the acquisition of the final adaptive result (correction of gas exchange and acid-base balance in tissues).

Our data on the correlation between cardiorespiratory functions are used in medical practice. Clinical trials on pregnant women, parturient women, and newborns with acid load [5] resulted in the development of new methods for rapid diagnostics of acidosis and alkalosis. The proposed methods were introduced into obstetrical practice in Cheboksary. This approach allowed us to reduce the necessity for forced ventilation of the lungs in newborns by 2 times. The use of these methods for rapid diagnostics of acid-base imbalance and evaluation of placental insufficiency resulted in a significant decrease in the perinatal mortality rate (from 8.4 to 6.76‰) and early neonatal mortality rate (from 3.23 to 1.86‰) in 2005-2007. The proposed methods hold much promise for the use in other areas of medical practice, which are associated with severe changes in gas exchange and acid-base balance.

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