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Neurogenic Vasoconstriction

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ABSTRACT

For a long time, the vasoconstrictor function of the sympathetic nerves, both phasic and tonic in relation to the vessels of the heart and brain, was questioned. It was believed that both of these basins (especially the coronary), in contrast to the peripheral and splanchnic channels, react to stimulation of sympathetic nerves by vasodilation or do not react at all (this provision was also included in the manuals on physiology). Constant neurogenic tone of the coronary and cerebral vessels was considered to be very insignificant. Finally, it should be recalled that, in their severity, cerebral and coronary vasoconstrictions are incommensurable with the narrowing of the vessels of the skin, resting muscles, and abdominal organs during reflex and centrogenous excitation of the sympathetic-adrenal system. Until recently, there was an almost traditional contradiction between neurophysiological data on the same type of efferent impulse in all vasoconstrictor nerves and circulatory indicators of a differentiated reaction of organ and regional blood flow. Recently, however, qualitative differences in efferentation have also been found. It is believed that the basis of such differentiated activation is the unequal level of tonic activity of the central neurons. However, the point is apparently not only that the reactions are thus performed at the centers. The receptor features of the regional vascular bed play an equally important role.

Keywords: Sympathetic Nerves; Vessels; Vasoconstriction

Introduction

For a long time, the vasoconstrictor function of the sympathetic nerves, both phasic and tonic in relation to the vessels of the heart and brain, was questioned. It was believed that both of these basins (especially the coronary), in contrast to the peripheral and splanchnic channels, react to stimulation of sympathetic nerves by vasodilation or do not react at all (this provision was also included in the manuals on physiology). Constant neurogenic tone of the coronary and cerebral vessels was considered to be very insignificant. This is explained by the fact that in both organs it is methodically very difficult, and sometimes fundamentally impossible (for example, when studying local cerebral blood flow), to separate the vascular and trophic (metabolic) effects of stimulation. Inert or discrete methods for recording blood flow did not make it possible to fix a rapidly passing vascular neurogenic reaction, but only prolonged functional hyperemia of a metabolic nature was recorded. Hence the idea arose of the negligible role of neurogenic influences on the cerebral and coronary vessels and of the leading role of metabolic factors in the regulation of their tone. Vascular reactions in response to stimulation of sympathetic nerves were considered almost exclusively as secondary metabolic vasodilation associated with increased organ function [1].

Modern methods of continuous recording of vascular regional tone and blood flow made it possible to capture purely neurogenic vascular reactions, but their absolute value (especially in vasodilation) turned out to be several orders of magnitude lower than metabolic reactions. So basically, the metabolic hypothesis has not been shaken [2]. Researchers of cerebral circulation have long been under the hypnosis of the phenomenon of autoregulation. The most precise definition of this important property of any regional vascular bed was given by Armstead, who pointed to its ability to regulate the blood supply of an organ in accordance with the needs or, in a narrower sense, the genuinal tendency of an organ (tissue) to maintain a

constant blood flow, arterial perfusion pressure despite changes in the removal of fielding. Does the nervous system take any part in the formation of this genuine tendency? From the very beginning, a negative answer was given since the phenomenon was completely preserved after deafferentation of the organ [3]. But it could not be otherwise since the standard study of autoregulation consists in taking essentially static characteristics of organ hemodynamics with stepwise changes in perfusion pressure. Under these conditions, the initial, rapid, component of autoregulatory responses to changes in systemic hemodynamics cannot be identified. It is these dynamic components of the autoregulation curve that can have a neurogenic nature. However, in the understanding of most physiologists, autoregulation continues to be a purely local process of blood flow adaptation due to metabolic and (or) vascular (smooth muscle) factors [4].

This is, in the most general terms, the current state of the problem of regulating the blood supply to vital organs and the role of the neurogenic factor in it. Interestingly, against the background of the skepticism of most physiologists about the real role of neurogenic vasoconstriction and vasodilation, the clinical literature (and even more practice) continues to exploit the concept of spasm of the coronary and cerebral arteries, especially in central autonomic disorders (coronary angioedema, etc.) [5]. This article presents experimental data on neurogenic vasoconstrictions of the cerebral and coronary vessels, the best ways to detect these reactions, their effector nature and possible functional significance for the whole organism. Does the cerebral vascular bed have significant neurogenic (sympathetic) vascular tone? Apparently, an unambiguous answer cannot be given due to the functional heterogeneity of different parts of the vascular network. The usual method for assessing adrenergic vascular tone is, as you know, desympathization. When registering the total volume of blood in the brain by the method of 131Xe clearance and the total blood flow to the brain with an electromagnetic flow meter, a distinct increase in blood flow (by 15-30%) was noted in the first 1-2 days after removal of the superior cervical ganglion. This coincides with the disappearance of norepinephrine from the tissue according to the histochemical fluorescence method. In the future, within 10-20 days, the blood flow gradually decreases to the initial level, which is associated with an increase in the sensitivity of vascular smooth muscles to circulating catecholamines common to all tissues. These facts have been obtained on monkeys, dogs, cats, goats and mice. They can be considered as an experimental basis for the operation of cervical sympathectomy, which is quite widely used in neurosurgery, to improve collateral circulation during occlusive processes in the main vessels of the brain [6]. However, the real magnitude and duration of the beneficial effect of the operation is unclear, since systematic studies of cerebral blood flow have not been conducted [7]. Less definite and pronounced effects of denervation in the study of local, especially pial, cerebral blood flow. Harper et al., using the 133 Xe clearance method, were able to obtain an increase in blood flow in the frontal-parietal region of monkeys after bilateral sympathectomy. In N. I. Girs (registration of local cerebral blood flow in the parietal region) and T. V. Baluyeva (registration of the total blood flow to the brain), a significant (by 40-50%) increase in blood flow was noted in the first hour after removal of the superior cervical ganglion in cats [8].

It can be assumed that innervation and a certain (rather moderate compared to other regions) degree of sympathetic vascular tone extend mainly to large arteries and arterioles of the brain. During denervation and irritation in different areas of the brain, various redistributive vascular reactions can occur to maintain a constant blood flow [3]. Although there is as yet no morphological evidence for the existence of special trophic sympathetic fibers for brain neurons, one can reasonably speak of the trophic function of postganglionic sympathetic cerebral vasomotors. This refers to the release of the mediator into the intercellular space and its effect not only on vascular smooth muscles, but also on the state of cell membranes and the permeability of the blood-brain barrier. Therefore, after the so-called desympathization of the brain by removing the superior cervical ganglia, one should theoretically expect not only circulatory, but also trophic changes in the brain tissue, manifested in metabolic shifts [7]. In the laboratory of L. V. Govorova, new interesting facts in this direction were obtained. In her experiments, 1, 7, 14, and 40 days after bilateral and unilateral cervical sympathectomy, microsomal and mitochondrial fractions of the rat brain were found to undergo metabolic changes, indicating both a change in the ion permeability of cell membranes and a violation of the process of oxidative phosphorylation. With unilateral sympathectomy, interhemispheric asymmetry of indicators was observed [9].

After the initial (apparently due to an operating injury) decrease in the intensity of respiration and phosphorylation, on the 14th day, an increase in the rate of consumption of O2 by mitochondria was observed at a constant rate of phosphorylation, which led to the well-known phenomenon of uncoupling of the processes of oxidation and phosphorylation (oxidation is not fully provided by ATP synthesis). as evidenced by a decrease in the activity of mitochondrial ATPase. In the same period, there was an increase in the activity of the membrane enzyme of the sodium pump - Na + -K + ATPase in the endoplasmic reticulum, apparently associated with the release of Na + from the cell and the entry of K + there [10]. Thus, already preliminary data indicate the dependence of a number of indicators of energy metabolism and active transport of ions in the brain on the state of its sympathetic innervation. So far, it is difficult to judge the intimate mechanisms of trophic influences. Perhaps they are associated with the action of catecholamines on cell membranes, possibly mediated by circulatory shifts. Nevertheless, it is obvious that as a result of the removal of the superior cervical sympathetic ganglion, the bioenergetic systems of the brain cells are unbalanced; according to a number of data, this increases their sensitivity to external influences (hypoxia) [11].

Desympathization of the heart by removal of the stellate nodes (the left ganglion is of primary importance) also generally leads to

an increase in coronary blood flow, which is eliminated by beta-blockade. The effect of denervation is explained by the removal of a-adrenergic constrictor tone and stimulation of beta receptors by circulating catecholamines. T. V. Baluyeva obtained the same effect in our laboratory. In her experiments on cats with registration of outflow from the coronary sinus within 1-2 hours after bilateral stellectomy and removal of the adrenal glands (which obviously leads to the release of catecholamines into the blood), a persistent increase in coronary blood flow was observed. It is noteworthy that against the background of this vasodilation, constrictor reactions of a hormonal nature are well manifested [12]. From a number of experimental data, it follows that sympathetic coronary vascular tone restrains and moderates metabolic and autoregulatory vasodilation. So, after removal of the left stellate ganglion, reactive hyperemia for a 10-second clamping of the coronary artery increases by 31% compared with the initial value, and after a-blockade by 23%. Experiments on the effect of stimulation of the sympathetic nerves on the course of the autoregulation curve of cerebral blood flow lead to the same conclusion [11]. A detailed consideration of the results of experiments with denervation is necessary not only for assessing sympathetic tone. After denervation, hormonal factors of vascular reactions are also detected. Vasoconstriction and vasodilation in response to nerve stimulation only indicate that this vascular pool is under potential neural control. However, most of the facts relating to neurogenic influences on the cerebral and coronary vascular bed were obtained in experiments with irritation of nerves, peripheral ganglia and nerve centers [13].

In the literature of recent years, the question of the existence of neural influences on the autoregulation (AP) of cerebral vessels has been repeatedly discussed. After denervation of the vessels, the AR is completely preserved, but the course of its curve shifts to the left. This means that autoregulatory vasodilation with a drop in perfusion pressure becomes more perfect and prolonged, and the breakdown of AR in the left part of the curve occurs later. On the other hand, denervated vessels cannot effectively resist an increase in perfusion pressure, and the AP curve breaks in this place earlier. The opposite phenomenon - a shift of the AR curve to the right - is observed when sympathetic nerves are stimulated [14]. It has been observed that at any given arterial pressure, cerebral blood flow is less in hemorrhagic hypotension (in which sympathetic activity is increased), than after reducing the pressure of pharmacological preparations. Consequently, in the left part of the curve, the sympathetic nerves act in the opposite direction to the AR, oppose it, and prevent vasodilation with a decrease in pressure. The tipping point at the top of the AP curve is also shifted to the right. This means that hypertension is better tolerated by the brain tissue and its vessels with an excited sympathetic. The brain is thus protected from hemorrhage, breakthrough of the blood-brain barrier and edema. Of course, the latter provisions should be considered as a working hypothesis, but the experiments underlying it deserve serious attention, since they are directly related to the functional significance of the innervation of the cerebral vessels [9].

Data on the importance of the vessels of sympathetic innervation of cerebral vessels for autoregulation (adaptation) of cerebral blood flow can be summarized as follows: excitation of the sympathetic system helps autoregulatory vasoconstriction with an increase in systemic pressure but prevents autoregulatory dilation from fully manifesting itself. Indeed, in unanesthetized dogs, only the preservation of sympathetic innervation in one half of the brain limits autoregulatory vasodilation in this half during acute hypotension. The removal of sympathetic tone helps vasodilation and, accordingly, prevents constriction. For example, on the side of the removed superior cervical ganglion, vasoconstriction caused by hyperventilation is weakened [15]. Continuing the analogy with the coronary bed, it should be recalled that irritation of the sympathetic cardiac nerves causes not only changes in vascular tone, but also transfers the exchange in the myocardium to a new, higher energy level, which in turn determines the characteristics of vascular reactions. The degree of trophic influences on the brain tissue during stimulation of the sympathetic nerves and desympathization is not yet clear; a wide field of research on the relationship between blood supply and function opens up here [16].

Finally, we should mention the shifts in the AR curve under the influence of alpha- and beta-blockers introduced into the brain. However, the concentrations of antagonists were high (1.5 mg/kg), which does not exclude the nonspecific effect of the drug on both the vascular wall and the brain tissue. In our laboratory, the study of the so-called fast phase of autoregulation of cerebral blood flow was started. It has already been mentioned above that the phenomenon of constancy and independence of cerebral blood flow from changes (within certain limits) of systemic arterial pressure was obtained at one time using discrete methods for recording blood flow and with stepwise changes in blood pressure. Subsequently, the use of methods for continuous recording of blood flow also made it possible to characterize the transient process of autoregulation during rapid pressure changes. It turned out that a rapid increase or decrease in pressure is accompanied by passive changes in cerebral blood flow, which returns to its original level and stabilizes only after a few minutes. For pathology, such a transitional phase is of particular interest, since it is at this time that hemorrhagic and ischemic consequences of abrupt changes in cerebral blood flow can be expected even with physiological, but fairly rapid changes in systemic pressure [17].

Naturally, the question arose about possible mechanisms for compensatory damping of a potentially dangerous transitional period. If such a fast phase of autoregulation, which counteracts the initial changes in cerebral blood flow, exists, it should be assumed that it is neurogenic in nature, taking into account the difference in the latent periods of myo- and neurogenic vascular reactions. Indeed, such a fast phase was obtained in the experiments of T.V. Balueva and V.B. Semenyutin. In acute experiments on cats under chloralose anesthesia with an RKZ-1 electromagnetic flow meter, the total blood

flow to the brain was recorded, and all extracranial branches of the external carotid arteries and the internal carotid artery were ligated. The system pressure drops were created by a pressure switch. Both an increase and a decrease in pressure by 20-60 mm Hg. Art. caused corresponding passive changes in cerebral blood flow. However, on average, after 5 s, he began to return to the initial level, despite the fact that blood pressure still continued to rise or fall (the further course of the classical autoregulation curve was not traced, since this was not the task of the study) [1,2,4,5].

The assumption about the neurogenic nature of the fast reaction was tested in 7 experiments with bilateral removal of the superior cervical sympathetic ganglia. By itself, sympathectomy led to a significant (by 56% on average) increase in cerebral blood flow, which coincides with the data on a pronounced sympathetic tone of the cerebral vessels, which was not disturbed by the conditions of the acute experiment and preparation. Nevertheless, 30 min after desympathization, the fast phase of autoregulation was completely preserved with the same latent average period. However, the conclusion that the nervous system is not involved in the rapid phase of autoregulation would be premature, since after sympathectomy the ascending noradrenergic intracerebral system remains intact and the conditions for reflex excitation of the stem centers persist with abrupt changes in systemic hemodynamics. Therefore, the exclusion of α-adrenergic receptors of vessels was used as the final link in neurogenic vasomotor reactions of any origin. Against the background of the action of dihydroergotamine (1 mg/kg into the carotid artery), the rapid phase of autoregulation in response to an increase in pressure was not observed in any experiment. For 51 ± 6 s, cerebral blood flow tracked a new, high, pressure level, after which the classic autoregulation reaction began [14].

These results make it possible to state in general terms the need for intact innervation of the cerebral vessels for the implementation of rapid adaptations of cerebral blood flow to changes in systemic hemodynamics [16]. Recent data on a decrease in the resistance of the vascular bed of the rat brain to hemodynamic stress against the background of α-blockade are in good agreement with the results of T. V. Balueva and V. B. Semenyutin. It is noteworthy that the reason for this lies, apparently, in the specific adrenoblockade of vascular receptors, and not just in a decrease in vascular tone. The myotropic vasodilator papaverine had no such effect. Cerebral vasoconstriction has been most fully studied during stimulation of the cervical sympathetic nerves. This material is also summarized in recent reviews on the nervous regulation of cerebral blood flow [18]. The blood flow recorded by various methods decreases by 5-15% on the side of irritation, mainly in the anterior parts of the brain. With continued irritation, the reaction stops after 20–80 s, which is associated with the depletion of mediator secretion. Vasoconstriction is significantly weakened or completely disappears against the background of a-blockade. The same reaction, independent of concomitant hypertension, was also noted with irritation of the stellate ganglion [6].

To detect cerebral vasoconstriction of a neurogenic nature, it is necessary to maintain a constant level of pH, pO2, pCO2 and exclude the influence of systemic hypertension. A fast passing reaction may not be recorded by discrete methods of measuring blood flow. Under these conditions, neurogenic vasoconstriction in the brain turned out to be insignificant in comparison with other organs and significantly less than the magnitude of the vascular response to changes in arterial blood pressure O2 and CO2. There is less information about cerebral constrictor responses to stimulation of the brainstem sections of the brain itself [2]. Traditionally, the concept of neurogenic cerebral vascular tone was extended to extraparenchymal (i.e., located outside the brain tissue) main and pial vessels, which corresponded to the known data on the high density of their sympathetic innervation. The intracerebral arteries, with their limited physical capacity for vasomotion, were considered to be the object of metabolic influences that provide working hyperemia of certain areas of the brain due to increased local neuronal activity. However, since 1965, the concept of the stem noradrenergic center for the regulation of cerebral hemodynamics has been developing. This refers to the accumulation of adrenergic neurons in the area of the so-called blue spot (locus coeruleus), the processes of which go in an ascending direction to the small hypothalamic and cortical vessels. It is noteworthy that the locus coeruleus, area postrema, pituitary and supraoptic nuclei are characterized by abundant vascularization and high permeability of the blood-brain barrier for catecholamines and angiotensin II [1].

With bilateral destruction of the area of the blue spot, the level of catecholamines in the hypothalamus, thalamus and parietal cortex decreased; local blood flow increased in the same areas. On the other hand, cervical sympathectomy does not lead to depletion of intracerebral vessels in catecholamines, although histologically, noradrenergic innervation of these vessels was also shown, mainly in the hypothalamus and parietal cortex. Two types of beta-adrenergic vasodilation are assumed here: associated with beta reception of the vascular wall itself and with neuronal activity mediated by cellular beta reception (this activity can be suppressed by barbiturates). Although histologically, noradrenergic innervation of these vessels was also shown, mainly in the hypothalamus and parietal cortex. Two types of beta-adrenergic vasodilation are assumed here: associated with beta reception of the vascular wall itself and with neuronal activity mediated by cellular beta reception (this activity can be suppressed by barbiturates). Although histologically, noradrenergic innervation of these vessels was also shown, mainly in the hypothalamus and parietal cortex. Two types of beta-adrenergic vasodilation are assumed here: associated with beta reception of the vascular wall itself and with neuronal activity mediated by cellular beta reception (this activity can be suppressed by barbiturates) [12].

It should also be mentioned that irritation of the locus coeruleus can be accompanied not only by beta-dilation, but also by a-constriction of intracerebral arterioles and precapillaries, accompanied by an increase in the permeability of brain tissues to water. Local application of a-blocker to the blue spot led to an increase in cerebral blood flow by 25% [16]. In practical terms, information about the a-receptor nature of spasms of the main arteries of the brain, caused by the application of blood or mechanical irritation, is very valuable. However, the mechanism of cerebral vasospasm apparently also includes serotonin and its specific receptors, for which α-blockade is ineffective. It has been experimentally shown that serotonin is generally the most powerful brain vasoconstrictor. With a-adrenergic receptor mechanism, they tried to connect the narrowing of cerebral vessels during hypocapnia, but this is not shared by everyone. Unilateral irritation of the uncut cervical sympathetic nerve was performed above the upper cervical ganglion and the head end of the cut (at the level of the fork of the carotid artery) vagus nerve. Irritation was carried out through bipolar silver electrodes with series of rectangular current pulses (5-20 Hz, 1.5 ms, 3-5 V for 30 s). Systemic pressure was recorded at the central end of the femoral artery. The pharmacological agents used for the analysis of reactions (atropine, a-blocker dihydroergotamine, beta-blocker obzidan) were administered intravenously at a dose of 1-2 mg/kg. To test the effectiveness of adrenergic blockade, adrenaline (10–30 μg) was also administered, and before the start of the experiment, heparin (3 mg/kg) [15].

Irritation of the sympathetic nerve was accompanied in all samples by an increase in perfusion pressure (i.e., a constrictor reaction of the cerebral bed) by 14.10.7 mm Hg. Art. with a latent reaction period of 3.2 0.5 s. The constrictor reaction reached its greatest value by the end of stimulation at the 30th second. Changes in systemic arterial pressure in this case were ambiguous: in 31% of samples there was an increase, in 13% a decrease by 17-18 mm, in the rest there were no changes. Dihydroergotamine completely blocked reactions to irritation of both systemic and perfusion pressure. It should be noted that against the background of a-blockade, which is known to act hypotensively, the initial perfusion pressure was maintained at the same level as before the blockade (122.3±8.9 mm), while the systemic pressure significantly decreased (from 127 to 52 mm). Beta-blocker obzidan (propranolol) did not affect the nature of vascular reactions in the brain. In response to stimulation of the head segment of the vagus nerve, cerebral vasoconstriction was also observed (an increase in perfusion pressure by 17.9–0.7 mm). At the same time, in most cases (63%) there was a depressor reaction of systemic pressure, in 33% - a pressor reaction. Alpha block also completely ruled out vasoconstriction [1-3]

As far as is known, cerebral vasoconstriction in response to irritation of the afferent fibers of the vagus nerve was obtained for the first time. It should be emphasized that in most cases a systemic depressor reaction typical of cats was observed. One could interpret this vasoconstriction as a consequence of retrograde irritation of the efferent adrenergic fibers running in the vagus trunk, however, there are sufficient grounds to believe that vagal efferentation also causes vasopressin vasoconstriction [19].

Irritation of the supraoptic nucleus in 21 out of 27 experiments (80% of trials) caused an increase in both systemic and perfusion pressure in the cerebral vessels with a latent period of 1–2 s. The reaction values were 25 ± 8 mm for perfusion pressure and 6 ± 7 mm for systemic pressure 36. In the remaining 6 experiments (20% of the trials), biphasic changes in cerebral vascular tone were observed [15]. Against the background of α-blockade, all pressor reactions did not appear at all in 1/3 of the experiments, and in 2/3 they turned into depressor reactions. Irritation of the posterolateral hypothalamus (25 experiments) led to an even more pronounced increase in blood pressure and cerebral vascular tone, and the a-blocker also removed or distorted these reactions. In contrast, stimulation of the preoptic zone caused either depressor or biphasic (-+) systemic pressure reactions, while cerebral perfusion pressure changed insignificantly and was not statistically significant. Naturally, the interpretation of the resulting cerebral vasoconstriction needs limitations imposed by the peculiarities of the technique. We can only talk about changes in the total (total) cerebral vascular tone under artificial conditions of forced autoperfusion of the pool with a constant volume of blood. As mentioned above, changes in tone do not reflect the state of blood supply to the brain as a whole or in its regions.

Nevertheless, as in the study of coronary sympathetic reactions, data on centrogenous cerebral vasoconstriction also indicate the involvement of the main arteries and arterioles of the brain in generalized adrenergic reactions, fundamentally similar to those observed with direct stimulation of the sympathetic nerves. Vasoconstriction, as shown by our experiments, is specific for stimulation of the supraoptic nucleus and posterior hypothalamus and is not observed during stimulation of the preoptic region. Coronary vasoconstriction during stimulation of the sympathetic cardiac nerves and stellate ganglions has been systematically recorded since the 1950s as an initial, rapidly passing reaction, followed by prolonged vasodilation of a metabolic nature. The main significance of these studies is that they showed the fundamental unambiguity of sympathetic influences on the coronary and peripheral vessels, contrary to the then widespread view of the sympathetic nerve as a coronary dilator and the vagus as a coronary constrictor [17]. As in other vascular beds, the α-adrenergic nature of coronary constriction was established, since the reaction did not occur after the administration of an α-blocker. Most clearly and naturally, a-constriction is detected against the background of beta-blockade of both inotropic effects (beta1-receptors) and vascular vasodilator (beta2-receptors). In chronic experiments on nonanesthetized dogs, Gregg et al. obtained clear evidence of sympathetic coronary

constriction. When registering coronary blood flow in different phases of the cardiac cycle with an electromagnetic flowmeter, already 2 s after the onset of irritation of the stellate ganglion, they observed a decrease in mean, diastolic and systolic blood flow against the background of an increase in the calculated coronary resistance. After 10–20 s (with continued irritation), the phase of increased blood flow and decreased vascular resistance began [2].

In numerous studies of the 60s and 70s, coronary constriction was found not only with direct stimulation of the sympathetic cardiac branches, but also with generalized excitation of the sympathetic-adrenal system. in the experiment, such excitation can be obtained both by stimulation of the brain stem formations, and reflexively. Of greater interest is the activation of the sympathetic system during the baroreceptor sinocarotid reflex. Activation of baroreceptors, i.e., removal of inhibitory impulses to the vasomotor center when the carotid is clamped, sharply increases the efferent flow of adrenergic impulses both to the heart and to resistive and capacitive vessels. One of the typical patterns of circulatory reactions occurs, organized by different levels of the central nervous system. It should be emphasized that such experimental models, in comparison with the effects of nerve irritations, are more adequate to those circulatory stresses that occur during hemorrhage, hypoxia, and other conditions [5]. As is known, under sympathetic circulatory stress, not only (and sometimes not so much) changes in minute volume occur, but also adaptive regional redistributions of vascular tone occur. What is the degree and direction of reactions of cerebral and coronary vessels?

The literature on the involvement of coronary vessels in the carotid sinus reflex is quite extensive. While there were no methodological possibilities for separating the nervous, metabolic, and hemodynamic influences on the coronary bed, an increase in coronary blood flow due to an increase in systemic pressure and activation of myocardial metabolism was taken as reflex vasodilation with a decrease in pressure in the carotid sinus. However, after stabilization of pressure, chrono- and inotropic effects, it turned out that a decrease in carotid pressure in anesthetized dogs causes a tendency to coronary constriction, which is indeed balanced and overcome in the intact heart by secondary metabolic vasodilation. As for the effect of an increase in sinus pressure on the coronary vessels, no regular changes in their tone were found. What was previously mistaken for vagal coronary constriction turned out to be a slowing of coronary blood flow with negative inotropy and bradycardia [12]. As already mentioned, changes in coronary blood flow were judged by the outflow from the coronary sinus, for which a polyethylene catheter was inserted through the ear of the right atrium into the sinus and fixed with a ligature around the ear. The outflowing blood passed through a dropper with a photocell and entered a reservoir located 10 cm below the level of the chest. From the second reservoir, located 50 cm above the animal, the heated blood returned to the femoral vein, and the equality of outflowing and inflowing blood was established. The number of drops per 10-second interval was converted into an outflow volume rate (ml/min) [2].

Arterial pressure recorded in the axillary artery was stabilized by a pressure switch consisting of a hermetically sealed glass vessel containing a thin-walled rubber reservoir filled with blood. The latter was attached to the abdominal aorta. An air pressure equal to the arterial pressure was created in a glass vessel. Hemorrhage was caused by the withdrawal of 20 ml of blood. The carotid arteries were clamped for 60 s on both sides below the bifurcation. Pressure and blood flow were recorded on a loop oscilloscope. Experiments with bloodletting (10) did not make it possible to obtain reliable data on the nature of the reaction of the coronary vessels and the involvement of the carotid sinus reflex in this reaction. Only in 9 out of 37 bloodletting samples did the blood flow decrease, which could also be explained by a drop in perfusion pressure at the orifices of the coronary vessels. In the remaining 29 samples, against the background of a systemic depressor reaction, an increase in coronary blood flow (by 39%) and a decrease in the calculated coronary resistance (by 42%) were found. As mentioned above, such data are often interpreted as evidence of the existence of a special coronary dilatory reflex with a decrease in systemic pressure (as opposed to peripheral vasoconstriction). However, in the experiments, the nature of the reaction did not change significantly after transection of the sinus nerves. Experiments with temporary occlusion of the carotid arteries gave more definite results. Although in some experiments coronary blood flow increased against the background of a systemic pressor reaction, this could be explained by an increase in perfusion pressure, since coronary resistance did not change. In most of the experiments, against the background of an even more pronounced pressor reaction (35.5±5%), a decrease in coronary blood flow by 25±8% and an increase in coronary resistance by 36.4±16% were observed. The heart rate did not change.

The detected coronary vasoconstriction could be explained both by a myogenic autoregulatory mechanism in response to an increase in perfusion pressure, and by a neurogenic one. To exclude the first factor, experiments were carried out with the stabilization of blood pressure. In most cases (24 samples out of 37), signs of coronary constriction were observed. Since vasodilation recorded in the remaining 13 samples could be associated with myocardial metabolic and neurogenic vasodilating effects, pharmacological heart blockade with obzidan (1 mg/kg) and atropine (0.5 mg/kg) was applied in the next series with stabilized systemic pressure. Coronary constriction was noted in all 28 cases. This reaction was not detected against the background of α-blockade with phentolamine (2 mg/kg). It should be recalled here that the elimination of vasoconstriction by an a-blocker is not evidence of a purely neurogenic nature of vasoconstriction, since the action of not only the mediator noradrenaline, but also

circulating catecholamines is blocked. Therefore, further research, described in the next chapter, concerned the hormonal link of coronary constriction.

From the material presented, it is obvious that, in principle, the reflex excitation of the sympathetic-adrenal system leads in the coronary bed to the same constrictor reactions as in other areas. There is no reason to assume the existence of specialized central neurons that provide selective coronary dilatation during massive sympathetic efferentation. The compensatory increase in blood flow is apparently determined at the peripheral level by metabolic factors. Probably, the degree of activation of the sympathetic system also matters. This may be related to the higher incidence of vasoconstriction with carotid occlusion than with phlebotomy. Under conditions of the whole organism, the final character of the reaction of the coronary vessels to the intensification of efferentation through the cardiac sympathetic nerves cannot be considered certain. It depends on a number of circumstances: the degree of excitation of the sympathetic system and the involvement of the hormonal link, the intensity of metabolic changes, myocardial inotropy, the ratio of alpha and beta receptors in the coronary bed, autoregulatory reactions. It is easy to see that most of these factors function in the efferent link of the reflex [19].

When discussing the results of the described experiments, it should be borne in mind that, in contrast to experiments with a change in pressure in an isolated carotid sinus, with bilateral carotid clamping, we are not dealing with baroreflex in its pure form. Sympathetic excitation is due not only to the removal of inhibitory impulses from baroreceptors, but also to cerebral ischemia and, to a certain extent, excitation of chemoreceptors. With regard to changes in vascular tone, all three factors are synergistic. With regard to cerebral ischemia, special models of neurogenic coronary spasm have been proposed with a decrease in perfusion pressure in the vessels of the brain and cessation of blood supply [4]. When discussing the regional distribution of vascular tone in the carotid sinus reflex, including coronary blood flow, they usually mean static characteristics in response to a step-like change in sinus pressure. Meanwhile, special attention should be paid to phase transition processes, since the task of arterial baroreceptors is precisely rapid adaptation [17].

Changes in cerebral vascular tone and blood flow in the carotid sinus baroreceptor reflex have been studied less well. Here, the need for a thorough study of phase transient adaptive processes with rapid changes in system pressure is especially prominent. There are multidirectional changes in cerebral blood flow in relation to changes in pressure in the carotid sinus. In other words, with a drop in pressure, cerebral blood flow increases presumably due to selective inhibition of sympathetic tone or activation of the cholinergic system. On the contrary, an increase in pressure in the sinus leads, according to the same authors, to the restriction of cerebral blood flow, while the peripheral vessels dilate [15]. The question of the participation of cerebral vessels in the pressor and depressor carotid sinus reflexes remains unclear. There are no electrophysiological studies that would indicate a specific (compared to other regions) efferent impulses in postganglionic sympathetic fibers to the cerebral vessels during a general excitation of the sympathetic system due to a pressure drop in the carotid sinus. The traditional idea of the uniformity of sympathetic efferentation in all departments, which originates from Cannon, is currently being revised both in electrophysiological terms and according to the data of organ physiologies of blood circulation. Nevertheless, many researchers are inclined to think that vasoconstriction is observed in the brain with a depressor carotid sinus reflex due to circulatory effects (as in coronary circulation) [18].

By changing the pressure in isolated sinuses in steps and measuring the cerebral inflow in the vertebral arteries in dogs with a flow meter, researchers showed unidirectional reactions of the cerebral vessels with peripheral ones: their expansion with increasing pressure in the sinus and narrowing with clamping of the carotid. Information about the complete loss of autoregulatory properties of the cerebral vessels (tracking changes in blood pressure) after complete denervation of the carotid sinuses, as far as is known, was not later confirmed x2ъ. If the reflex excitation of the sympathetic-adrenal system makes it possible to reproduce the features of blood circulation in vital organs under circulatory stress, then the study of the effects of hypothalamus irritation on coronary blood flow can be considered as a partial model of cerebrocardial syndrome. The direct reactions of coronary vascular tone and blood flow to stimulation of the hypothalamic centers are fundamentally similar to the effects of stimulation of the sympathetic nerves and are realized through these nerves.

Naturally, the task does not include consideration of the anatomy and function of the hypothalamus as a regulator of vegetative processes. As is known, the division of the hypothalamus into anterior parasympathetic and posterior sympathetic, based on the data of Karplus and Kreidl, Gellhorn and Hess, does not quite correspond to reality due to mutual overlap and the lack of clear boundaries between the pressor and depressor zones (according to changes in blood pressure during stimulation), the dependence of the effect on the frequency of the irritating current, various regional changes, etc. Now it is more correct to speak of predominantly vasoconstrictor and predominantly vasodilatory zones. In the anterior hypothalamus, the vasoconstrictor zone includes the supraoptic nucleus and then extends caudally and laterally to the subthalamus (zona incerta and trout fields H1 and H2). In the posterior hypothalamus, the vasoconstrictor zone has stereotaxic coordinates: A from 8 to 10, L and H from 0 to 3. The effects of stimulation of these zones in relation to the ECG, rhythm and contractile function of the heart have been well studied. Studies of the coronary circulation during stimulation of the hypothalamus are few, but they reflect the same evolution of views on the role of sympathetic activation, which we traced on the example of stimulation of the nerves themselves. In the first works, only a long-term increase in blood flow was found against the background of a pressor reaction and excitation of the heart [13].

Later, an initial pressure-independent vasoconstriction on stimulation of the posterior hypothalamus was recorded (with a rotameter in dogs), which was reproduced by irritation of the stellate ganglion and the administration of adrenaline and blockade of beta receptors. These changes, recorded by an electromagnetic flow meter, did not correlate with either myocardial systolic tension or heart rate, from which the authors conclude that a decrease in blood flow is the primary response to nerve stimulation [14]. Let us dwell briefly on the efferent pathways of vasoconstrictor influences from the hypothalamus. Along the lateral walls of the 3rd ventricle of the brain from the medial parts of the hypothalamus are amyopiatic periventricular fibers. After turning in the caudal direction, these fibers pass into the central gray matter of the Sylviian aqueduct and further in the form of fasc. longitudinal dorsalis - to the bottom of the 4th ventricle. Here, synapses are formed with the neurons of the vasomotor center. Along the way, there are numerous collaterals into the reticular formation of the trunk. From the lateral hypothalamus and mamillary bodies through the mamillo-tegmental tract, the fibers descend into the lateral part of the reticular formation, forming here numerous synapses. Through the tegmentum of the brain, the nuclei of the anterior hypothalamus are also connected with the reticular formation [2].

Apparently, most vasoconstrictor neurons of the hypothalamus have synapses in the reticular formation (including the vasomotor center). After its destruction, vasoconstrictive influences from the hypothalamus are not carried out. In contrast, cholinergic vasodilating fibers from the anterior hypothalamus do not have a break in the reticular formation [4]. The second switching of vasoconstrictive impulses is carried out on the vasomotor neurons of the spinal cord. Such a polysynaptic character is manifested in the ratio of the frequencies of stimulation of the centers and efferent impulses in the autonomic nerves. With an optimal frequency of stimulation of the hypothalamus for the vasoconstrictor effect of 50-100 Hz, the frequency of efferent discharges in the fibers of the cervical sympathetic and lower cardiac nerves increases from 1-2 (normal tonic activity) to 7-9 Hz. A linear dependence (20-25: 1) of the frequency of efferent impulses in the cardiac nerves on the frequency of the hypothalamus is shown. This effect is based on the rhythm transformation during polysynaptic transmission [16]. Below the medulla oblongata, the vasoconstrictor pathways appear to partially decussate. Only bilateral sympathectomy removes the pressor effects of irritation of the anterior hypothalamus. Unilateral removal of the sympathetic chain, even in combination with hemisection of the spinal cord on the opposite side, does not have such an effect [17].

Constriction of the coronary and cerebral vessels is part of the general sympathetic vasoconstrictor reaction upon stimulation of the hypothalamus. At the same time, in relation to the cerebral vessels, in addition to the classical pathway (through the vasomotor neurons of the spinal cord and the sympathetic chain), there apparently exist intracerebral pathways for the transmission of vasoconstrictor influences. As far as is known, cerebral vasoconstriction during hypothalamic stimulation under conditions of desympathization has not been studied. However, some circumstantial evidence suggests the existence of this type of transmission. In particular, in the clinical observations of G. S. Tigliev, cerebral vasoconstriction with mechanical stimulation of the hypothalamic region during neurosurgical operations persisted even against the background of ganglionic neurovegetative blockade. An alternative explanation, hormonal factors for vasoconstriction, is discussed in the next chapter. In experiments on anesthetized cats, we studied the effect of hypothalamic stimulation through stereotactically inserted bipolar electrodes on coronary blood flow, recorded thermographically in the left descending artery. Irritation of the supraoptic nucleus and posteromedial hypothalamus (supramamillary zone) led to a pronounced (by 49 mm Hg on average) pressor reaction. Against its background, in $^{1}/3$ experiments (11 out of 38) a decrease in blood flow was observed in the first 10-15 seconds of stimulation. This reaction occurs both with intact vagus nerves and after vagotomy. Vasoconstriction was completely prevented by α-blockade with dihydroergotoxin and yohimbine, and against the background of α-blockade, blood pressure decreases in response to irritation, and dilation is observed in the coronaries.

Preliminary (a few days before the experiment) denervation of the adrenal glands, which excludes the release of adrenaline, does not change the pressor reaction in response to hypothalamic stimulation, but coronary constriction does not manifest itself in this case. A small material of observations (12 experiments) did not allow at that time (1967) to draw definite conclusions about the role of endogenous adrenaline in coronary constriction. However, the results of experiments with denervation of the adrenal glands, as well as with the removal of the pituitary gland, in which the pressor response to hypothalamic stimulation was preserved, led us to a general conclusion about the leading role of the neurogenic factor in hypothalamic constrictor reactions [8]. Desympathization of the heart in the form of removal of stellate ganglions ruled out coronary constriction in response to hypothalamus irritation, while dilator responses began to be observed more frequently. After denervation of the heart (stellatectomy and vagotomy on both sides 1-2 hours before the experiment), coronary reactions generally disappear. Here we should briefly present the results of works in which the method of denervation (desympathization) of the heart was used to prove the existence of neurogenic tone of the coronary vessels. Desympathization of the heart itself leads to an increase in coronary blood flow and a decrease in coronary resistance. Pericoronary denervation also increases coronary blood flow and decreases myocardial O2 uptake. The narrowing of the range of adaptation of the coronary blood flow to an increase in peripheral resistance was also described by other authors who used desympathization. After stellatec- tomy, there is no vasoconstriction in response to carotid clamping [9].

Systematic studies of general and regional cerebral blood flow after vascular desympathization have not been carried out either in

the experiment or in the clinic. So, a number of studies have shown that centrogenous sympathetic adrenergic vasoconstriction caused by irritation of the brain stem structures also extends to the coronary bed. This coronary constriction in the experiment is detected more often when blocking vasodilator factors opposing it, mainly metabolic ones in the myocardium. However, it would be premature to consider these experimental data as a model of neurogenic coronary spasms. Very perfect compensation mechanisms - hemodynamic, metabolic and neurogenic - are aimed at maintaining adequate coronary blood flow. Apparently, in the violation of compensatory adaptations, one should look for the nearest mechanisms of coronary insufficiency [9]. The situation is more complicated with the assessment of sympathetic cerebral vasoconstriction. So far, a moderate degree of constriction of cerebral vessels during stimulation of sympathetic pre- and postganglionic fibers is quite reliable. Bearing in mind the complex structure of the cerebral vascular bed, one cannot speak of a decrease in cerebral blood flow in general. Rather, it implies a restriction of blood flow to the brain due to an increase in tone and constriction at the level of the main arteries and arterioles. Local cerebral blood flow can change ambiguously due to redistributive reactions, although, apparently, one should attach importance to a decrease in regional volumetric blood flow in the anterior parts of the brain during sympathetic stimulation. The question of the participation of the brain bed in systemic constrictor reactions, not yet developed.

The problem of cerebral and coronary vasoconstriction is also significant from the methodological point of view. The fact is that the ideas about the exclusively vasodilator function of the sympathicus in these organs were largely based on teleological considerations about the inappropriateness and fatality of the constrictor responses of the vessels of the brain and heart. Meanwhile, this is far from being the case [12-,14,16-19,8]. An increase in arterial tone, vasoconstriction and restriction of blood flow do not in themselves indicate a lack of blood supply. Due to compensatory redistributive reactions, local blood flow can be maintained at the proper level. Neurogenic vasodilatory mechanisms opposing vasoconstriction are also aimed at this. In general, the lack of blood supply to an organ can only be judged by a violation of its function. In the first place in terms of importance here should be put the content of O2 in the venous blood flowing from the organ. An increase in the arteriovenous difference in O2, due to an increase in O2 uptake, is a sign of tissue hypoxia that occurs with vascular spasm, for example, with angiotensin and vasopressin [11-14,16-18].

What, then, is the functional meaning of sympathetic vasoconstriction of the cerebral and coronary vessels? To answer this question, one should obviously look in the experiment for such physiological situations in which neurogenic effects on the vessels (both constrictor and dilator ones) become significantly significant (not necessarily quantitatively!) in comparison with traditional metabolic factors. Based on the fact that neurogenic reactions are always realized faster than metabolic ones, one would expect them to appear if it is necessary to quickly adapt regional hemodynamics to changes in systemic hemodynamics. We are talking about the so-called fast (presumably neurogenic) component of AR, understood more broadly than the metabolic smooth muscle reaction. We also recall that sympathetic stimulation shifts the upper limit of AP to the right, and this theoretically should contribute to greater resistance of the brain vascular bed to systemic hypertension. The most adequate experimental proof of this assumption should be the demonstration of greater stability of the innervated vascular bed of the brain compared to the denervated one in case of sharp changes in systemic arterial pressure. In experiments, an experimental model of the gravitational load along the axis of the body of the animal (non-anesthetized rats) in the direction of the head-pelvis during rotation on a centrifuge was used. During rotation, the blood drains into the lower half of the body, and the pressure in the cerebral vessels drops to zero. After a sharp stop in rotation, the blood moves in the opposite direction and arterial pressure in the upper half of the body rises sharply, as a result of which hemorrhages in the brain tissue should be expected. Theoretically, a certain degree of cerebral vasoconstriction can counteract such a hemodynamic shock. Can it be provided by the metabolic and myogenic mechanisms of AR? Apparently not, since these same mechanisms, when the cerebral arteries are empty, ensure their maximum expansion and, being relatively inert, are unlikely to provide a quick and effective narrowing of the arteries with a sudden rise in pressure. Here, the neurogenic (fast) component of AP could be effective [17].

The considered theoretical assumptions were tested on animals in which the superior cervical sympathetic ganglia were removed on one side a day before centrifugation. It turned out that already after a load of 8 g, subarachnoid hemorrhages (visually) and parenchymal hemorrhages (histologically) were observed on the denervated side of the brain, localized mainly in the rostral forebrain, at the junction of the parietal and frontal lobes. At a load of 18 g, subarachnoid hemorrhages were observed over the entire surface of the brain, but parenchymal hemorrhages continued to be detected only on the side of denervation. In the intact (innervated) hemisphere, they appear only after a load of 22.5 g, also in its rostral sections. The fact of an increase in the threshold of hemodynamic shock tolerance while maintaining the innervation of the cerebral vessels should be specially noted. In all 18 rats hemorrhage in the brain parenchyma appeared after loads three times greater than the loads that were sufficient for hemorrhages on the denervated side of the brain [20]. Obviously, when pressure falls in the upper half of the body, activation of the vasoconstrictor sympathetic nerves of the head occurs due to the depressor carotid sinus reflex, activation of the chemoreceptors of the aortic arch and sinus, and brain hypoxia. As a result, the innervated vessels meet the hemodynamic shock in a state of greater constriction than the denervated ones. Here again, neurogenic mechanisms limit myogenic and metabolic autoregulatory vasodilation. From the experiments described, another important conclusion follows about the fundamental unambiguity of reflex changes in the tone of intracranial (cerebral) and extracranial vessels. Indeed, a special

series of experiments conducted by Sh. S. Tashaev showed that after a gravitational load, the same hemorrhages occur in the tissues of the denervated rat auricle (since the shell is supplied not only with fibers from the upper ganglion, the entire cervical sympathetic chain was extirpated for its denervation) [16].

In the next series of experiments, «hemodynamic shock» was modeled on 8 cats in an acute experiment under Nembutal anesthesia. Rapid pressure drops in animals were created by taking blood from a catheter inserted into the abdominal aorta, followed by reinfusion. With pressure fluctuations thus obtained from 20 to 160-170 mm Hg. Art. in cats with the superior cervical ganglion removed an hour before the experiment, Evans's blue was released into the tissue of the denervated hemisphere in the same areas where hemorrhages were noted in rats. If cats were preliminarily functionally desympathized by intravenous administration of the a-blocker phentolamine (4 mg/kg), then in response to pressure drops, bluing into the tissue was observed both on the denervated and on the intact side. The barrier function again increased after stimulation of the head end of the cut sympathetic. On the other hand, in hemorrhagic hypotension in goats, autoregulatory expansion of cerebral vessels was more perfect after a-adrenergic blockade, which relieves sympathetic tone (shift of the lower border of the AR to the left) [15].

Thus, even now, with sufficient grounds, one can speak of the protectionist role of the sympathetic innervation of the cerebral vascular bed. The task of further research is to identify and demonstrate the physiological situations in which neurogenic influences become significant in comparison with traditional metabolic factors.

As far as is known, the question of the functional significance of sympathetic coronary constriction has not been specifically raised. However, from a number of experimental data it clearly follows that the constrictor effects of adrenergic fibers to a certain extent moderate the dilatory action of metabolites in the vessels of both the heart and skeletal muscles. In the heart, the vessels of which must always be in a state of «sympatholysis», sympathetic innervation limits the possibility of expanding the coronary bed. This is manifested in a greater severity of reactive hyperemia after clamping of the coronary artery in dogs with a removed left stellate ganglion.

Coronary constriction caused by the administration of the α-stimulant phenylephrine or beta-blockade with competitive excitation of α-receptors also reduces metabolic coronary dilatation (eg, in response to forced cardiac pacing). It is important to emphasize here that this sympathetic coronary constriction ultimately leads to a decrease in myocardial pO2. Perhaps this is the main significance of the sympathetic innervation of the coronary vessels: the protection of the heart from the consequences of excessive «metabolic fire» and «malignant» metabolic vasodilation. Let us sum up some results and try to evaluate the significance of new experimental facts on neurogenic vasoconstriction of the vessels of the heart and brain obtained over the past one and a half to two decades. First of all, it can be considered completely established that sympathetic vasoconstriction in the brain and heart exists and, in its mediator and receptor mechanisms, does not fundamentally differ from the corresponding vasoconstriction in the skin, muscles, and internal organs of the abdominal cavity. The old ideas, according to which the sympathetic dilates the coronary vessels, and the vagus constricts them, have undergone a complete revision. With a sharp increase in sympathetic impulses in the cardiac nerves, the coronary dilatory effect is secondary, metabolic, and manifests itself at a later date than the primary constriction [10,11,13,14].

Neither the coronary nor cerebral vasoconstrictions discussed here represent either redistributive hemodynamic reactions or catastrophes in terms of functional consequences for the supplied organ. These reactions are short-lived; they are opposed by perfect vasodilatory mechanisms, not only metabolic, but also neurogenic. Neither physiologists nor pathologists have clarified the circumstances under which a short-term constriction can turn into a long-term vasospasm. A sign of it should be considered increasing tissue hypoxia, manifested in an increase in the arterio-venous difference in O2. According to a number of experimental data, it should be assumed that spasm cannot be provided by prolonged tonic impulses in the nerves; for its implementation, the addition of a stable humoral vasoconstrictor is necessary [7,10,11,13].

Finally, it should be recalled that, in their severity, cerebral and coronary vasoconstrictions are incommensurable with the narrowing of the vessels of the skin, resting muscles, and abdominal organs during reflex and centrogenous excitation of the sympathetic-adrenal system. Until recently, there was an almost traditional contradiction between neurophysiological data on the same type of efferent impulse in all vasoconstrictor nerves and circulatory indicators of a differentiated reaction of organ and regional blood flow. Recently, however, qualitative differences in efferentation have also been found. It is believed that the basis of such differentiated activation is the unequal level of tonic activity of the central neurons. However, the point is apparently not only that the reactions are thus performed at the centers. The receptor features of the regional vascular bed play an equally important role.

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