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Adrenergic Agents

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ABSTRACT

There are numerous contradictory publications on the effect of adrenergic substances on cerebral circulation. Researchers' great interest to this issue is explained by an extremely important role of the sympathetic-adrenal system in the regulation of cardiovascular system function and the wide introduction of various adreno stimulant and adreno blocking substances into medical practice. Thus, the possibility of pharmacological effects on cerebral blood flow and metabolism through its dopaminergic structures has been revealed in the experiment. The increase in cerebral blood flow under the influence of dopaminergic mimetics is consistent with clinical observations which indicate that the cerebral blood flow of the patients treated with haloperidol has the tendency to decrease. The question of the link between dopamine- and alpha-adrenergic (possibly also serotonergic) structures in the regulation of cerebral circulation requires further study.

Keywords: Cerebral Circulation; Adrenergic Agents

Introduction

There are numerous contradictory publications on the effect of adrenergic substances on cerebral circulation. Researchers' great interest to this issue is explained by an extremely important role of the sympathetic-adrenal system in the regulation of cardiovascular system function and the wide introduction of various adreno stimulant and adreno blocking substances into medical practice.

Adrenaline and Noradrenaline

These substances, as the main representatives of catecholamines, served as a favorite subject for studying the role of the sympathetic-adrenal system in the regulation of cerebral circulation. However, the results of the studies have led to controversy, which can be partially explained by differences in dosage, ways of drug administration, research techniques, as well as significant changes in blood pressure levels. In experiments on animals, a lot of researchers have noted an increase in cerebral blood flow and dilation of the pial vessels when medium and large doses of adrenaline and noradrenaline are administered intravenously. The effect is explained by a significant increase in arterial pressure, which caused passive dilation of brain vessels and increased blood flow. There were cases when even intraarterial injection and local application of catecholamines to the brain surface had no significant cerebrovascular effect. On this basis, it was often concluded that catecholamines have no direct effect on brain vessels or their effect is very insignificant. Most clinicians hold a similar opinion, because catecholamines did not cause a significant change in human's cerebral blood flow or slightly increased it. Some increase in cerebrovascular resistance after intravenous administration of catecholamines was explained by autoregulatory cerebrovascular response to increased blood pressure [1].

Along with these data, there is strong evidence in favor of the existence of constrictor reaction of cerebral vessels arising from the introduction of catecholamines. Earlier it was noted that in most cases local application of catecholamines caused constriction of cerebral surface vessels [2]. Administration of adrenaline or noradrenaline into the lumen of the carotid or vertebral arteries in doses that did not cause a significant increase in blood pressure was usually accompanied by cerebral vasoconstriction and decreased blood flow [3]. The vasoconstrictor effect of these substances on cerebral vessels was particularly pronounced under conditions of stable perfusion pressure or cerebral vascular resistography [4].

In our study [5] intravenous administration of adrenaline or noradrenaline (10 μg/kg) significantly increased the cerebral blood flow volume velocity by 50±11% and 45±16%, respectively, and increased Rho2 in brain tissue by 22±8% and 39±10.6%. Maximum manifestation of the effect was observed at the 1st minute and coincided with the moment of a sharp increase in arterial pressure. The dependence of blood flow changes on arterial pressure has been revealed in experiments with the stabilization of perfusion pressure using a special device [5]. Under these conditions, intravenous administration of adrenaline and noradrenaline in the same doses reduced cerebral blood flow by 52± 6% and 51±1% respectively. The effect was most pronounced at minute 1-2 and lasted 7-9 min, then it increased in some experiments. Such biphasic effect was more characteristic of the action of adrenaline.

In experiments with resistography [5] adrenaline and norepinephrine caused a clear increase in perfusion pressure from the intracranial and extracranial vessels. Having increased the volume of perfusion system (the technique proposed by V. M. Khayutin in 1958 to reveal direct and indirect effects of pharmacological substances) we observed a delayed response of perfused vessels, indicating a direct vasoconstrictor effect of the drugs. According to rheoencephalography data, there were no significant changes in the rheographic wave amplitude under the influence of norepinephrine, but changes in its shape indicated an increase in cerebral vascular tone. Thus, the results of our experiments, as well as the data of the other authors who applied the method of resistography or perfusion pressure stabilization, indicate a direct cerebrovascular constrictor response to adrenaline or norepinephrine. In recent years the direct vasoconstrictor effect of catecholamines has been confirmed in experiments on isolated strips and segments of brain vessels of animals and humans [6]. Convincing data on the direct effect of noradrenaline on brain vessels were obtained by Yu. E. Moskalenko et al. in the experiments of 1975 and 1977. The authors injected different doses of noradrenaline in animals (monkeys, cats) through special microcannulas implanted into the brain cortex tissue under conditions of a chronic experiment. It was noted that norepinephrine at a dose of 1-2 μg/kg narrows vessels and decreases blood flow in the cerebral cortex, and at a dose of 0.01 μg/ml causes vasodilation of cerebral vessels.

The increase in the tone of brain vessels under the influence of adrenaline and noradrenaline is due to the excitation of alpha-adrenoreceptors, which has been shown in several studies using various alpha-adrenolytics. In our experiments, prior administration of dihydroergotamine to animals completely eliminated or significantly weakened the constrictor effect of catecholamines. The perverse effect of adrenaline observed under these conditions (vasodilation) can be explained by the presence of not only alpha-, but also beta-adrenoreceptors in the brain vessels and extracranial vessels of the head. The latter remained sensitive to adrenaline after exposure to dihydroergotamine. Against the background of alpha-adrenolytic administration, norepinephrine, as a rule, did not cause a perverse reaction, which corresponds to the generally accepted opinion about the low sensitivity of beta-adrenoreceptors to norepinephrine with high sensitivity of alpha-adrenoreceptors to this drug.

In the literature one can often find statements that the response of brain vessels to catecholamines depends on a number of factors. H. Taeschler et al. (1952) observed that animals under chloralose anesthesia reacted to adrenaline and noradrenaline with a decrease in cerebral blood flow, while animals anesthetized with barbiturates had no changes in blood flow or passive changes due to hypertension occurred. According to Borkovskaya (1969), adrenaline increases non-anesthetized cats' blood filling of the brain cortex and decreases the anesthetized ones. When the cervical sympathetic nerve is irritated, vascular responses in the cerebral cortex are almost 2 times weaker for narcotized cats [7]. It seems that the depth of anesthesia and the nature of the narcotic substance can change the response of the brain vessels quantitatively rather than qualitatively. Qualitative changes in the response probably arise as a result of impaired ventilation and a corresponding shift in the blood gas composition. In our experiments with controlled breathing, the constrictor response to adrenaline and noradrenaline was maintained under hexenal, chloralose-urethane, and ether anesthesia, as well as in non-narcotized animals (local anesthesia and muscle relaxants).

Some studies have noted the dependence of cerebrovascular reactions to various pharmacological substances, especially catecholamines, on the concentration of CO2, O2 blood pH and CSF. Thus, under conditions of hypercapnia or hypoxia, the constrictor effect of catecholamines on brain vessels can disappear or decrease or a perverse (dilatatory) reaction occurs [8]. Under hypocapnia, noradrenaline causes cerebral vasoconstriction and decreased cerebral blood flow, apparently as a result of increased sensitivity of adrenergic vascular structures. A sharp decrease in the sensitivity of brain vessels to norepinephrine has been revealed with a decrease in the pH of the intercellular medium of the brain and blood. The data on the ability of prostaglandins and their biosynthesis inhibitor indomethacin to significantly change the reactivity of brain vessels to norepinephrine injection and sympathetic nerve stimulation are of great interest [9]. The possibility of participation of group E prostaglandins in the mechanisms of adrenergic regulation of cerebral circulation is admitted.

The question about the influence of catecholamines on the metabolic activity of the brain is controversial. According to some authors [10], catecholamines increase functional and metabolic activity of the brain and increase the consumption of O2. I. V. Golubeva (1967) noted an increase in pO2 in brain tissue under the influence of adrenergic substances, apparently as a result of an increase in cerebral blood flow. In our study [5], adrenaline and noradrenaline (10 μg/kg intravenously) increased pO2 in brain tissue mainly due

to the increase of cerebral blood flow, as the same doses of catecholamines did not cause significant changes in pO2 in brain tissue when the blood flow to the brain was stabilized. Some authors deny the direct influence of catecholamines on brain metabolism, as these substances poorly penetrate through the blood-brain barrier [11]. Nevertheless, some changes in brain metabolism under the influence of adrenaline (rather than norepinephrine) can be expected due to the stimulation of beta-adrenoreceptors. Probably, the changes in the functional and metabolic activity of the brain under the influence of adrenaline are reflected to a certain extent in its cerebrovascular effect. However, we cannot agree with the opinion of some researchers, who consider the effect of catecholamines on brain vessels as an indirect reaction in response to a change in the functional or metabolic activity of the central nervous system (CNS).

As noted above, the increase in cerebrovascular resistance under the influence of catecholamines is often explained by the autoregulatory response of the brain vessels aimed at maintaining a stable blood supply to the brain. Although the physiological mechanism of autoregulation has not been definitively elucidated, two concepts are widely accepted: myogenic and metabolic ones. If we assume that brain vessels are insensitive to catecholamines, then the very increase in intravascular pressure during general catecholamine hypertension from the perspective of the myogenic concept will cause cerebral vasoconstriction. It can also be assumed that a passive increase in cerebral blood flow at the beginning of hypertension will lead to a rapid removal of vasodilator metabolites from the brain, an increase in PH and vascular resistance due to cortical alkalosis [12], i.e., the metabolic mechanism of autoregulation will work. It is possible that autoregulatory constriction in response to increased perfusion pressure under the influence of catecholamines accompanies their specific vasoconstrictor action, since autoregulation is maintained when catecholamines are injected into brain vessels [13]. However, it cannot play a crucial role, as cerebral vasoconstriction under the influence of catecholamines is clearly manifested with stabilized perfusion pressure or stabilized blood flow to the brain. E.S. Gabrielyan and A.M. Garper in 1969 and 1973 showed that with a moderate decrease in blood pressure, not yet causing a decrease in cerebral blood flow, intravenous norepinephrine administration led to a decrease in blood flow. It is impossible to explain this by autoregulation. Despite the great similarity of vascular action of adrenaline and norepinephrine, some differences have been noted. Thus, experimental and clinical observations have shown that norepinephrine has a stronger constrictor effect on brain vessels than adrenaline [14]. Low doses of adrenaline sometimes cause active vasodilation of brain vessels.

Reactions of brain vessels, extracranial head vessels, peripheral and other vascular basins to catecholamines differ significantly [15]. Norepinephrine caused, as a rule, a more pronounced constrictor reaction of peripheral vessels compared to cerebral vessels. A similar effect was observed when high doses of adrenaline were administered, whereas in low doses it often induced multidirectional vascular responses. These differences, as well as the phasing of vascular responses to adrenaline, can be explained by the different sensitivity of alpha- and beta-adrenoreceptors to catecholamines and their unequal distribution in the vascular system of a body. According to W. Rosenblum in 1973, the adrenergic nerves of the brain vessels bind norepinephrine more actively than the nerves outside the brain. He also thought that this could explain the relatively insignificant response of the brain vessels to exogenous noradrenaline or sympathetic nerve irritation. The data on the sensitivity of different segments of the cerebral vascular system to adrenomimetics are of great interest. G.I. Mchedlishvili in 1960 using differential manometry revealed a narrowing of the main (internal carotid and vertebral) cerebral arteries under the influence of adrenaline. Subsequently [16] a similar effect of norepinephrine was observed under the conditions of the original method of internal carotid artery resistography. The vasoconstrictor effect of this substance was also observed in experiments on spiral strips of different segments of canine and human brain arteries.

Thus, improvements in techniques have revealed a constrictor effect of the sympathetic-adrenal system on cerebral vessels, although it has not been generally recognized yet as the role of the system in the regulation of cerebral circulation remains unclear. There are a number of factors intrinsic to cerebral vessels more than to other vessels that may significantly influence the cerebrovascular effect of catecholamines. Tyramine. Tyramine is not known to exert a direct adrenomimetic effect but does so through the release of noradrenaline from tissue reservoirs. Tiramine is inferior to norepinephrine in strength of its vasoconstrictor action but superior in duration. After sympathetic denervation or respiration, the vasoconstrictor effect of tyramine is significantly reduced or completely disappears. There is evidence that intracarotid administration of tyramine does not cause significant changes in cerebral blood flow and O2 consumption under normocapnia [17]. However, under hypercapnia (RAS2 60 mm Hg) tyramine significantly reduces cerebral blood flow. It is believed that under normocapnia tyramine does not penetrate through the blood-brain barrier, so its cerebrovascular action is not manifested.

A detailed analysis of the effect of tyramine on cerebral and extracranial vascular tone was performed by E.S. Gabrielyan and co-workers in 1976. It is noted that intracarotid injection of the drug increases cerebrovascular resistance and decreases regional cerebral blood flow. There was a biphasic reaction in extracranial vessels and total arterial pressure. First there was short-term vasoconstriction and increased blood pressure, then they were replaced by prolonged vasodilation and decreased blood pressure. Repeated injections of tyramine during the same experiment progressively decreased the pressor effect and deepened the depressor effect. The appearance of the vasodilatory phase can be explained

by tachyphylaxis phenomena and the formation of ontopamine, a product of tyramine hydroxylation. The authors attribute great importance to tyramine in the pathogenesis of a migraine attack.

Mesaton

In general, there are not many studies on the effect of mesaton on the cerebral circulation. According to our results [5], intravenous injection of mesaton (0.01 mg/kg) to anesthetized cats increased perfusion pressure (resistography method) in brain vessels by 15±2.6% and arterial pressure by 21±3.8%. In experiments with parallel registration of intracranial and extracranial vascular tone, mesaton (0.1 mg/kg intravenously) increased intra- and extracranial vascular tone by 36±5.03% and 31±4.6%, respectively. According to rheoencephalography, mesaton reduced the amplitude of the rheographic wave by 29±5.2%, causing smoothing of its apex and displacement of the dicrotic tooth, which also indicated an increase in cerebral vascular tone. The volume velocity of cerebral blood flow after intravenous administration of mesaton at a dose of 0.05-0.1 mg/kg increased by 27±3% in most experiments. The maximum manifestation of the effect coincided with a period of significant increase in blood pressure. After a few minutes, the blood flow decreased by a value lower than the initial one, despite the fact that the blood pressure was still above the initial level. The initial increase in blood flow was due to a significant increase in systemic arterial pressure, as evidenced by experiments with perfusion pressure stabilization. Under these conditions, intravenous administration of the same doses of mesaton reduced cerebral blood flow by 24±3.5% without a preceding increase phase.

Thus, mesaton clearly increases cerebral vascular tone, but the volumetric blood flow rate depends to some extent on the level of arterial pressure. When blood pressure is significantly elevated, blood flow increases despite an increase in cerebrovascular resistance. When blood pressure is unchanged or moderately increased, cerebral blood flow under the influence of mesaton decreases. Preliminary administration of dihydroergotoxin (0.5-1 mg/kg) or phentolamine (0.5-1 mg/kg) to animals completely eliminated or significantly attenuated the cerebral vascular response to mesaton. Consequently, the vasoconstrictor effect of this substance is realized through alpha-adrenoreceptors.

Ephedrine

According to some authors [18], ephedrine increases cerebral blood flow by increasing blood pressure. In our experiments [5], intravenous injection of ephedrine at a dose of 0.1mg/kg to anesthetized cats increased perfusion (resistography method) by 19±3.1% (P<0.001) and total blood pressure by 26±3.496 (P<0.001). When the drug dose was increased to 0.5-1 mg/kg, these values were 39±6.5% (P<0.001) and 60±13.3%(P<0.001), respectively. According to rheoencephalography, the same doses of ephedrine reduced the rheographic wave amplitude by 18±5.596 (P<0.05). In some experiments, the decrease in amplitude was preceded by a brief increase in amplitude. The apex of the wave often became smoothed, the dicrotic tooth was shifted upwards. The noted changes indicate an increase in cerebral vascular tone under the influence of ephedrine. Despite the increase in cerebrovascular resistance, the volume velocity of cerebral blood flow after intravenous injection of ephedrine at a dose of 0.5-1 mg/kg did not decrease, but rather increased by an average of 47%. This is due to a significant increase in arterial pressure. Under conditions of stabilized perfusion pressure, ephedrine at the same doses reduced cerebral blood flow volume velocity by an average of 27±4.5% (P<0.001). Prior (4 and 24 h before the experiment) administration of reserpine (rausedil) at a dose of 1-1.5 mg/kg attenuated the constrictor response of brain vessels and the overall hypertensive response to ephedrine. Against the background of administration of alpha-adrenolytics (diproergotoxin or phentolamine), the effect of ephedrine was either insignificant or wasn't observed at all; sometimes a perverse response (dilatation instead of constriction) was noted. It may be assumed that the realization of constrictor cerebrovascular action of ephedrine is due to its indirect sympatho-mimetic influence.This is evidenced by inhibition of vasoconstrictor action of ephedrine not only by alpha-adrenolytics, but also by sympatholytics.

Isadrine

Most researchers have not noted significant changes in humans' cerebral blood flow after a single injection of various beta-adreno-stimulating substances [19]. In experiments on animals' intra-arterial injection of beta-adrenomimetics increased cerebral blood flow [20]. A similar effect was also observed with intravenous administration of the same substances in doses not causing a significant decrease in arterial pressure [21]. In conditions of hypercapnia the vascular effect of izadrin weakened [22], apparently due to the decrease of arterial blood pH. Local application did not significantly change the diameter of the pial vessels [23] but prevented the spasm of the pial arteries under the influence of local application of barium chloride or electrical and mechanical stimulation. According to our data [24], intravenous administration of izzadrin (1- 5 mcg/kg) to anesthetized cats with a stable blood volume in conditions of autoperfusion of brain vessels reduces perfusion pressure by 36.6±2.69%. Under separate perfusion of intracranial and extracranial vessels, intraarterial administration of yzadrn (0.005 μg/mg) decreased perfusion pressure in these vascular basins by 15.4±2.6% and 30±3.5%, respectively. Isadrine increased the rheoencephalographic amplitude by 122, 7±15,1 %. At first, after intravenous treatment with izadrine there was a short-term decrease of cerebral blood flow volume by 26,5±4,9%, because of significant (by 49,4±4,5%) decrease of blood pressure, afterwards blood flow rapidly increased and exceeded the initial level by 18±8,3% during the 5th minute, though blood pressure did not always reach the initial level. A similar pattern of changes was observed in pO2 in the brain tissue. In experiments with stabilized perfusion pressure, there was no initial phase of cerebral blood flow decrease. Follow-

ing administration of izzadrin at the same dose (5 μg/kg), cerebral blood flow increased by41.5±7.1%. Consequently, changes in cerebral blood flow under the influence of izzadrin depend on the value of arterial pressure and the vasodilator response of cerebral vessels to the drug. Prior blockade of the beta-adrenoreceptors with anaprilin (0.3 mg/kg intravenously) significantly reduced or completely eliminated the effect of ichadrine on intracranial and extracranial vascular tone and pO2 in the brain tissue.

Thus, the results of our studies confirm the data of other authors on the dilatatory response of cerebral vessels to ichadrin, which is realized by means of beta-adrenoceptors. Apparently, the distribution of these receptors or their sensitivity to ichadrine in different vascular basins is not the same. Clopheline. The effect of clopheline on cerebral circulation has been little studied. A large number of materials are dedicated to the study of its influence on systemic arterial pressure in hypertension. The mechanism of hypotensive effect of the drug is considered in detail in a 1978 monograph by A. V. Waldman. A lot of researchers have concluded that the hypotensive effect of clopheline is associated with the excitation of alpha-adrenoreceptors of central adrenergic neurons, which have an inhibitory effect on the vasomotor center of the medulla oblongata.

V. Sankina studied the effect of clopheline on anesthetized cats' arterial pressure, tone of cerebral and peripheral vessels under the conditions of resistography technique. It was found out that intravenous administration of the drug at a dose of 2 μg/kg to an animal increased the tone of cerebral vessels by 19.7±5.8 %. The effect was manifested immediately after the drug administration, and it was most pronounced at 1-2 min and lasted until the end of the experiments (60-90 min). Femoral vascular tone changed differently within 5-7 min after clopheline administration: it decreased in some experiments, increased in others. Later there was a vasodilator reaction of the femoral vessels, which lasted until the end of the experiments. Blood pressure in most experiments first showed a short-term increase followed by a gradual progressive decrease, which at 60-90 minutes was 40-50% of the initial level. Increasing the clopheline dose to 10 μg/kg resulted in an increased constrictor response of the cerebral vessels and some attenuation of the dilator effect from the femoral vessels, especially in the later terms of observation, whereas the overall hypotensive effect remained approximately the same as at the lower dose (2 μg/kg). Prior blockade of alpha-adrenoreceptors with dihydroergotanin attenuated or eliminated vascular responses to clopheline. Thus, the results confirm the alpha-adrenomimetic character of vascular reactions to clopheline. A persistent increase in cerebral vascular tone with a pronounced general hypotensive effect is noteworthy. Such divergence is of interest from both theoretical and practical points of view and requires further study.

Dopaminergic Agents

It is known that dopamine is one of the important neurotransmitters of the brain [25]. Recently, dopaminergic innervation in the cerebral cortex has been revealed to be particularly abundant in the caudate nucleus. It has been noted that some pharmacological substances (dopa, dopamine, apomorphine) selectively excite dopaminergic receptors, while others (pimozide, haloperidol) block them. In experimental studies it has been shown that intravenous administration of apomorphine increases cerebral blood flow, increases brain O2 and glucose consumption [26]. The increase in blood flow upon stimulation of dopaminergic receptors is mediated by a metabolic mechanism. Pimozide in the doses that completely blocked the action of apomorphine did not affect blood flow and brain metabolism and did not change the response of brain vessels to CO2. It is concluded that the initial indices of the total cerebral blood flow and metabolism do not depend significantly on the activity of dopaminergic units in the CNS. The results of a comparative study of the direct action of dopaminergic substances on brain vessels in vivo and in vivo correlate well with changes in the cerebral blood flow [27]. It was noted that application of apomorphine to the brain surface in low concentrations (0.1-10mcg) caused dilation of pial vessels; higher concentrations did not enhance the vasodilatory effect, but, on the contrary, caused vasoconstriction. The vasodilatory response persisted after blockade of beta-adrenergic and cholinergic receptors, indicating the involvement of dopaminergic receptors. The vasoconstrictor effect of high concentrations of apomorphine, according to L. Edvinsson, is mediated through alpha-adreno- and/or serotonin receptors.

A study of brain O2 consumption [28] showed that stimulation of dopaminergic receptors by intravenous administration of L-dopa, D-amphetamine or apomorphine caused a significant increase of pO2 in the cortex and cerebral blood flow. Dopamine had no effect because it does not penetrate the blood-brain barrier. Blockade of dopaminergic receptors with haloperidol or pimozide depressed the observed increase in pO2 in the cerebral cortex. Alpha-adrenergic blockade with phenoxybenzamine also eliminated the oxygenating effect of dopaminergic agonists. It is believed that the dopaminergic mechanism may play a role in the regulation of 02 brain consumption. Thus, the possibility of pharmacological effects on cerebral blood flow and metabolism through its dopaminergic structures has been revealed in the experiment. The increase in cerebral blood flow under the influence of dopaminergic mimetics is consistent with clinical observations which indicate that the cerebral blood flow of the patients treated with haloperidol has the tendency to decrease [29]. The question of the link between dopamine- and alpha-adrenergic (possibly also serotonergic) structures in the regulation of cerebral circulation requires further study.

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