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PERMEABILITY OF BLOOD BRAIN BARRIER FOR CARDIOTROPIC SUBSTANCES UNDER HYPOTHERMIA AND HYPERTENSION

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SUMMARY

It has been shown that under hypothermia conditions the interactions between central and autonomous contours of cardiac activity regulation can be significantly changed, therefore the probability of paradoxical reactions of an organism to application of cardiotropic preparations increases. The change of a sign of chronotropic effect of cathecholamines (CA) and acethylcholine (AC) under hypothermia in a great extent is substantiated by an increase of blood brain barrier (BBB) permeability, that should be taken for consideration in practical medicine. Besides therapeutic cooling regimens contribute to a recovery of impaired rhythmicity of functioning of nerve and cardiovascular systems, in particular under conditions of emotional stress, that is one main causes of human disease appearing.

KEY WORDS: central nervous system, cardiovascular system, hypothermia, rhythmic old effects, catecholamines, blood brain barrier, emotional stress

INTRODUCTION

Nowadays it is obvious, that under stresses of different genesis the BBB permeability considerably increases [1]. In this connection it is very curious, that the absence of data on BBB functional state in many current conceptions of general adaptational syndrome.

As any highly productive scientific idea, the problem of stress, being classical one, is not already a dogma [1-3, 6-11]. Thereat the most general critical remarks were referred to the most important notion of the conception - about non-specificity of stressoric reaction. Today the majority of investigators consider, that neuroendocrinic reaction of an organism to truly different stressors is various. Nevertheless in the stress theory as an adaptive syndrome with an alternate domination of catabolic and anabolic processes is one general for all stressors and in this case non-specific peculiarity or regularity, that some authors call as "adaptational process wave-likeness law" [10]. Practically in any quite a complete work devoted to the problem of a stress one can find multiple evidence of a wave-likeness of adaptational reactions, when the period and amplitude of initial rhythm with following damping increases, a decrease in this period with following recovery of initial rhythmicity [9-11]. It is known, that the term "stress" was adopted from physics by Kennon and Selier [7]. The maintaining of rhythms complicated hierarchy even in a physical system means the presence of synchronizing mechanism. There is a sense to suppose, that in mammalians a special functional system, controlling and directing the adaptational period rhythmicity in its both specific and non-specific manifestations (specific regulation of non-specific "driving" in the setting points of special homeostasis parameters) was formed.

Certain temperature variations may be the most physiological, an adequate stressor for such a system, because a special role in the regulation of organism structural and functional rhythmicity belongs to thermosensitive processes,- the first link in the estimation of the accordance of chaos and order degree in an organism's inner medium and environment [3]. Such a system is progressively developing in the evolutional process and, probably, functioning in a full extent only in homoiothermal organisms, which gained with homoiothermia the perception ability of inner medium entropic characteristics, because thermosensitive mechanisms may be integrated with the thermostatic ones. Therefore up to the present time the generally used stress conception continuing to be based on general principles of reflex theory (stimulus-response), the majority of experimental data testify, that stress manifests as a branched system of an organism's response [9-11]. In organization of its rhythmic pattern from our point of view the BBB participates for example by means of regulation of blood barrier balance of para- and sympathomimetics [4, 5]. It is apparently that of working frequences of thermoreceptors and BBB resonance frequency band in the range of second rhythm ultraslow bioelectric brain activity, determining synchronization of the functioning of main homeostatic mechanisms [1,3-5]. Here it is appropriately to refer to remote, but quite a fundamental work of Hoff [9], where the author showed his ideas about the variational character of symptomatic and parasymptomatic tonus and "complete vegetative switching" during different extreme ef-

fects. It is necessary to note, that Hoff does not make his scheme absolute, by truly assuming the possibility of complicated dynamics of para- and the alternation of asympathic reactions depending on the stimulus intensity and quality, that find its confirmation in the later works of other authors [10-13]. Such processes are convenient to study be means of the example of cardiac and vascular system at hypothermia, supposing, that various cooling programs may stimulate different versions of sympathic and parasympathic effects. "Mild" stress of medical hypothermia is able to start the pendulum of homeostatic reactions stopped by "hard" effect during the adaptation failure [1].

An efficient application of medical craniocerebral hypothermia (CCH) during different pathologies of cardiac and vascular system stipulates the usage of the complex of medical substances. However under the conditions of CCH the interactions of central and autonomous contours of cardiac activity regulation [1-5] may considerably change, that increases the possibility of paradox organism responses to the application of cardiotropic preparations. This is stipulated by the fact, that under the autothermal conditions the series of substances, non-penetrating through BBB, possesses an opposite effect at systemic and central ways of introduction [5]. An organism cooling causes cardinal rearrangements of brain neurodynamics, resulting in an increase in BBB permeability. So, on hypothermia background the change of signs of CA bathmo-, dromo-, ino-, tono-, chrono-, cardiotropic effects [8] and an increase of sympathic effect of substances, possessing manifested parasympathic effects.

In this connection the effect of norepinephrine (NE), adrenaline (A), acetylcholine (AC) on the frequency of cardiac pulsations (CPF) at different levels of BBB permeability of cooled brain after emotional stress.

MATERIALS AND METHODS

Experiments were conducted on white rats of the mass of 200-250g. Functional state of BBB was estimated by radioisotopic method at rhythmic hypothermia with the effect frequency 0,1-0,2 Hz (0,1RH, 0,2RH) and kHz [1, 3-5], that was carried-out by means of programmable cooling device, designed in the Special Designing and Productional Bureau with Experimental Unit of the institute for problems of cryobiology & cryomedicine of the National Academy of Sciences of the Ukraine. Rhythmical hypothermia was conducted by means of the set-up, consisting of electrogenerator and electroencephalographer, connected to platting board potentiometer, where a carriage was changed to a shutter to stop the flow of cold air (-4- -6°C), being supplied in the cameras with animals by industrially manufactured hypotherm. CPF was estimated by means of cardiogram, being registered by the BST-1 electroencephalographer in the second standard removing with the further mathematical processing 100-500 cardiointervals. Variational pulsography and spectrum-correlational analysis of ECG were carried out. The following indices were calculated: mode (Mo), mode amplitude (MoA), variational swinging-off (ΔX), the index of regulatory system tension ($TI=Amo/2\Delta X \times m_0$), index of vegetative equilibrium ($VEI= Amo/\Delta X$), vegetative rhythm index ($VRI = 1/m_0 \times \Delta X$), I_k-the second value of autocorrelation function; m_o - argument of the first negative value of autocorrelation function - slow waves of the first order (Sm), slow waves of the second order (So) [2]. Arterial hypertension was modulated by the method of emotional stress by means of making pain irritations by electric current to animals' group (15s - effect, 45s -break) during 30 min in each of 18 days.

The results of the experiment have shown, that under hypothermia upto 35°C and below 30°C, CA introduced into a blood channel increase palpitation, but during injection into an anterior hypothalamus part result in RHB slowing. However there is a temperature range (32°C±1°C), where a systemic CD introduction causes a central effect, i.e. E and NE do not increase, but decrease RHB (Table 1). This fact can testify to the increase in the BBB permeability for given substances, that was confirmed by radioisotopic investigations. It has been shown, that during animal cooling down to 32° C the BBB permeability increases more than twice for ^{3}H-A and ^{3}H-HA, which under normothermia, surfacial or deeper hypothermia did not penetrate into a brain (Table 1.). In order to reveal more fine reguliarities during these procedures the analysis of a cardiac rhythm with the enrolling of special mathematical means was accomplished. It has been revealed (Table 2), that the indices of mathematical analysis of cardiac rhythm at CCH reflect different forms of regulation processes. An increase in Mo (points to the most probable level of blood circulation system functioning) during a slightly changed variational span ΔX (the index, connected with the activity of parasympathetic nerve system) and M_o amplitude (the index, reflecting a mobilizing effect of cardiac rhythm control centralization, stipulated by the effect of vegetative nerve system sympathetic compartment testifies to the considerable rearrangements in the mechanisms of sympathetic and parasympathetic regulation links. Low values of I_k, m_o (which physiological matter consists in the estimation of the degree and character of central contour effect to the autonomous

one), S_o (reflecting the activity of control intersystemic level) and S_m (characterizing the state of subcortical nerve centers), as well as IN decrease (characterizing the vegetative homeostasis shift) testify to the parasympathetic nerve system predominance. By our opinion under hypothermia conditions these changes can be related with CA penetration into hypothalamus, where they cause a parasympathetic effect on the centers of cardiovascular system. Consequently, statistical characteristics of dynamic series of cardiointervals under hypothermia can testify to the change in hypothalamus BBB permeability for CA.

Table 1

CCH effect on RHB and BBB permeability at a systemic introduction of catecholamines

Experiment's conditions	Rate of the heart's beat (% of the norm)		BBB permeability coefficient (Cp)	
	A	HA	^{3}H-A	^{3}H-HA
Control	120 ± 3	115 ± 2	0.06 ± 0.01	0.16 ± 0.05
CCH 35°C	115 ± 5	110 ± 5	0.07 ± 0.01	0.17 ± 0.06
CCH 32°C	75 ± 3*	80 ± 3*	0.27 ± 0.02	0.3 ± 0.06*
CCH 28°C	112 ± 5	109 ± 6	0.05 ± 0.009	0.15 ± 0.04

Notes: A-epinephrine hydrochloride (0.1% solution, 0,5 ml /100g); NE-norepinephrine hydrochloride (0,2% solution, 0,5 ml/100 g);
^{3} N-A - 20µl of solution 1µ Ki/1µl; Kp - the ratio of specific brain radioactivity to blood specific radioactivity;
*- differences in comparison with the control are statistically significant (P<0.05)

Table 2

The effect of rhythmic hypothermy on BBB permeability and RHB at the background of a systemic introduction of NE and AC

Pharmacological background	Parameters	Duration 0,1, ЂС, min			
		0	45	65	85
NE	RHB, % of the norm	115±5	110±4	60±5*	105±6
^{3}N-NE	Kp	0.13±0.04	0.2±0.05	0.5±0.04*	0.19±0.05
AC	RHB, % of the norm	80±5	120±6*	80±5	75±5
^{3}N-AC	Kp	0.12±0.03	0.45±0.01*	0.18±0.05	0.2±0.06

Notes: AC - acethylcholine chlorous 10 mg/100g; NE-norepinephrine hydrochloride (0.2% solution, 0.5 ml/100 g);
^{3}N-AC - 5µl, 1µKi/1µl; Kp - the ratio of specific brain radioactivity to blood specific radioactivity;
* - differences in comparison with the control are statistically significant (P<0,05)

It is necessary to note, that under CCH conditions a significantly statistical increase in RHB on the background of a systemic AC introduction was not revealed. However this fact can not testify to a low BBB permeability for AC under normothermia, because AC central effect might be "masked". AC in contrast to CA causes among with a negative, slight positive cardiotropic effect. It has been demonstrated, that vagus nerves cause on a heart both negative and positive dromo-, ino-, chronotropic effects, obviously stipulated by switching preganglionic fibers not only to cholinergic ones, but to the adrenergic intracardiac neurones [4]. Therefore the interactions of CA and AC "cardiac effects" were studied under rhythmical hypothermia too, capable to more strongly activate BBB in comparison with CCH [2,3].

The investigation results demonstrated, that to the 45th and 65th minute of a cold effect during ЂС and NE systemic inroduction the central effect on RHB was respectively observed, i.e. NE did not increase, but decreased, and ЂС did not inhibit, but accelerated the palpitation (Table 3). During NE injection at the background of 0,1 RH RHB reduces linearly, although it resembles so-called negative stair (Wudvords's phenomenon [4]). In the same cases during AC introduction the RHB changes have a quasi-sinusoidal character by the type of a positive stair (Boudichi's phenomenon [4]). Moreover, the periods of RHB increase are changed by the decrease in a cardiac rhythmicity, as a rule with 0,1-0,2 Hz frequency, tracing by a comlicate way the rhythm of a cold effect. Such effect of a neurotransmitter on RHB dynamics at 0,1 RH should reflect in a known extent the peculiarities of BBB permeability. The analysis of radioisotopic investigations demonstrated, that a common level of BBB permeability during a rhythmical hypothermia was almost twice higher, than at a classical CCH, but the permeability maxima for ^{3}H-HA and ^{3}H-AX were corresponded on different stages of 0,1 RG in a complete correspondence with the moment of their central ef-

fects (Table 2). We can suppose, that the processes of BBB permeability for AC and NE are spreaded in a space and time. BBB permeability for NE basing on its central effect in a cardiac rhythm is explained by "sluice mechanism", i.e. a successive mechanism of the system opening of constantly existing channels (for example, in the field of endotheliocytes dense contacts). RHB dymanics during a systemic AC injection testifies to its entering into a brain might be provided by the appearance of temporary transendothelial channels, passing through a neuromediator with a second rhythmicity.

An increase in BBB permeability during hypothermia is obviously biologically significant. A physiological expediency of this increase consists in the "support" necessity of a strengthened functioning of the brain predominating neurotransmitter processes by coming from blood CA as the local neurohormones.

Thus, the paradoxal cardiotropic effects during hypothermia are in a considerable extent stipulated by an increased level of BBB permeability. The probability of such phenomena is vitally important to take into consideration in a practical medicine when performing hypothermia with a medicinal purpose. To another hand, it was interesting to use a specific effect of a "mild stress" of cooling trigger regimens for "smoothing" consequences of " hard", for example, emotional stress. The information on the state of central contours of blood circulation control, in particular, of an autonomous one, stipulated by the interaction of a sympathetic and parasympathetic compartments of nerve system, is given one of the methods of mathematical analysis of a cardiac rhythm - variational pulsography. The hypertension, caused by an emotional stress, is accompanied with the following changes of cardiorhythmographic indices (Table 3). The predomination of sympathetic regulation of a cardiac rhythm is observed, that is manifested in a decrease in cardiac interval distribution mode, an augmentation in the mode amplitude, an increase in the index of a vegetative balance, the rhythm vegetative index and a tension index.

Table 3

Statistical indices of the dynamic series of cardiointervals at hypothermia and hypertension

Indices	Mo	ΔX	AMo	TI	VEI	VRI	I_k	m_0	Sm
Hypothermia	157.9 ± 7.2*	108.7 ± 3.1	115.5 ± 4.2*	66.3 ± 6.4*	43.8 ± 3.3**	54.6 ± 6.1**	27.3 ± 5.1**	27.8 ± 4.8**	70.8 ± 6.6*
Hypertension	76.4 ± 6.1*	110.5 ± 3.1*	135.9 ± 5.2*	120.2 ± 4.4*	111.1 ± 3.3*	120.2 ± 5.4*	20.1 ± 7.1*	26.4 ± 6.4**	60.4 ± 6.3*

* - differences in comparison with the control are statistically significant (P<0.05),
** P < 0,01

Side by side with this the disturbance of the shape of distribution curve was observed. It was assymetric with the decreased RR intervals prevailing, that testify to the presence of transition processes of more manifested tachycardia. When studying the shape of distribution curves it was elucidate, that the majority of them sharply differs on the normal distribution of accidental values, that is characteristic for intact animals in a rest. More detailed investigation of the processes of blood circulation central regulation processes is possible by means of correlational and spectrum analysis of cardiac rhythm (Table 3). Autocorrelational analysis of cardiointerval series in hypertensive rats demonstrated a sharp decrease of autocorrelational function, characterizing a weak series organization, prevailing of autonomic contour regulation of cardiac rhythm. During a spectral analysis a considerable decrease of waves energy with a big period, characterizing a sharp depression of the highest levels of blood circulation regulation (control contours A and B according to [2]). Obviously, the processes on the Barcroft effect progressively developed (a decrease of parameters variability, characterizing the state of physiological functions). A sharp dynamics disturbance of BBB permeability for NA and AC (phase coincidence entering into a brain). Phenomena of such kind in any case resulted in a failure of adaptive abilities of cardiovascular system to a stable hypertension (>200 mm of mercury column), frequent death of animals (upto 50%).

Resonance amplification of antiphase oscillations of BBB permeability for sympatho- and parasympathomimetics under hypothermia of hypertensive animals triggerred a natural rhythmicity of BBB functioning, in this case a stable normalization of blood pressure occured. However only further serious study of neurophysiology of trigger regimens of hypothermia of mammalians will demonstrate the perspective of their usage in clinic.

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ПРОНИКЛИВІСТЬ ГЕМАТОЕНЦЕФАЛІЧНОГО БАР'ЄРА ДЛЯ КАРДІОТРОПНИХ РЕЧОВИН ПРИ ГІПОТЕРМІЇ І ГІПЕРТЕНЗІЇ

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РЕЗЮМЕ

Показано, що в умовах гіпотермії значно змінюються відносини центрального й автономного контуру регуляції серцевої діяльності, у зв'язку з чим підвищується вірогідність парадоксальних реакцій організму на застосування кардіотропних препаратів. Зміни знака хронотропного ефекту катехоламінів (КА) і ацетилхоміна (АХ) при гіпотермії залежить від підвишеної проникнивості гематоенцефаліч-ного бар'єра (ГЕБ), що необхідно ураховувати в практичній медицині. Разом з тим лікувальні режими охолодження допомагають відновленню порушеного ритму центральної нервової і серцево-судинної системи, особливо в умовах емоційного стресу, однієї із причин виникнення захворювань людей.

КЛЮЧОВІ СЛОВА: Центральна нервова система, серцево-судинна система, гіпотермія, ритмічні холодові впливи, катехоламіни, гепатоенцефалічний бар'єр, емоційний стрес

ПРОНИЦАЕМОСТЬ ГЕМАТОЭНЦЕФАЛИЧЕСКОГО БАРЬЕРА ДЛЯ КАРДИОТРОПНЫХ ВЕЩЕСТВ ПРИ ГИПОТЕРМИИ И ГИПЕРТЕНЗИИ

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РЕЗЮМЕ

Показано, что в условиях гипотермии могут существенно изменяться взаимоотношения цельтрального и автономного контуров регуляции сердечной деятельности, поэтому повышается вероятность парадоксальных реакций организма на применение кардиотропных препаратов. Изменение знака хронотропного эффекта катехоламинов (КА) и ацетилхолина (АХ) при гипогтермии в значительной степени обусловлено повышением проницаемости гематоэнцефаличекого барьера (ГЕБ), что необходимо учитывать в практической медицине. Вместе с тем лечебные режимы охлаждения способствуют восстановвлению нарушенной ритмики фунционирования нервной и

сердечно-сосудистой системы, особенно в условиях эмоционального стресса, одной из основных прияин возникновения заболеваний человека.

КЛЮЧЕВЫЕ СЛОВА: центральная нервная система, сердечно-сосудистая система, гипотермия, ритмичные холодные влияния, катехоламины, гематоэнцефалический барьер, эмоциональный стресс