the partial pressure of oxygen in blood flowing from the left ventricle of the isolated heart is always greater than in blood flowing from the right heart. The data given above suggest that coronary blood does not drain into the capillaries of the myocardium but is shunted along arterio-luminal and arterio-sinusoidal vessels into the left chambers of the heart. The present investigation showed that the magnitude of this shunt can change substantially within relatively short intervals of time. Drainage into the left chambers of the heart increases considerably under conditions of hypoxia and ischemia. It can therefore be considered that, in pathology of the heart accompanied by these conditions, the appearance of considerable shunting of coronary blood into the left chambers of the heart can aggravate the oxygen hunger of the myocardium and lead to the development of attacks of angina.

The results also indicate that it is impractical to assess the blood supply to the myocardium from the inflow of blood into the coronary arteries alone. Acute insufficiency of the myocardial blood supply may evidently arise in the presence of a normal, or even increased, blood flow in the coronary arteries, should a considerable flow of arterial blood along the shunts directly into the chambers of the heart appear.

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# POSSIBLE CORRECTION OF BRAIN ENERGY METABOLISM IN NEUROSES BY NICOTINIC ACID DERIVATIVES


V. I. Kresyun



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KEY WORDS: nicontinic acid; brain energy metabolism; neuroses.


Pharmacologic control of CNS functions in neuroses, permitting a systemic approach to their analysis, is important from both theoretical and practical points of view. One of the main manifestations of neurosis is a disturbance of energy metabolism and neurochemical processes that lie at the basis of mechanisms of psychological adaptation [2, 3]. Any unfavorable influence acting on the body automatically involves energy metabolism. In neurosis any extraordinary load, even of emotional character, which has a psychological basis somehow or other is managed through the state of the energy systems of the neuron [6, 8]. There is thus a definite need for the creation and pharmacologic study of new psychotropic drugs to control the course of nervous processes at the level of brain energy metabolism. Tranquilizers now available and widely used, especially benzodiazepine derivatives, despite their marked stress-protective effect, themselves inhibit brain energy metabolism [9, 12].

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N. I. Pirogov Odessa Medical Institute.


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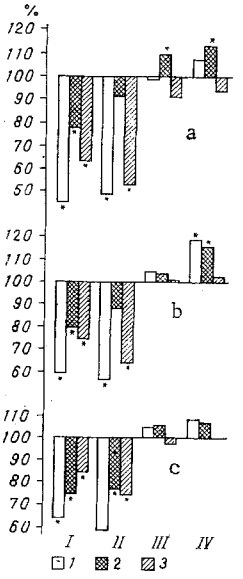


Fig. 1. Oxidative phosphorylation of brain structures during neurosis and pharmacologic correction. a) Cortex; b) limbic system; c) medulla. 1) ΔP; 2) ΔO; 4) P:O. I) Stress; II) chlordiazepoxide; III) nikogamol; IV) litonit. *P < 0.05 compared with control.

TABLE 1. Dynamics of Changes in Nucleotide Pool in Brain Structures of Rats with Chronic Neurosis and Receiving Prophylactic Treatment with Tranquilizers (in μmoles/g tissue)

| Experimental conditions | ATP | ADP | AMP | Total nucleotides | Atkinson's coefficient |
|---|---|---|---|---|---|
| | | | Cortex | | |
| Control | 1,439±0,067 | 0,708±0,013 | 0,408±0,005 | 2,555±0,071 | 0,70±0,008 |
| Stress | 0,650±0,017* | 0,210±0,009* | 0,604±0,005* | 1,464±0,024* | 0,51±0,005* |
| Chlordiazepoxide (2 mg/kg) | 0,951±0,038** | 0,901±0,016** | 0,293±0,008** | 2,145±0,037** | 0,65±0,005** |
| Nikogamol (10 mg/kg) | 1,303±0,040** | 0,601±0,018** | 0,301±0,007** | 2,214±0,037** | 0,73±0,005** |
| Litonit (10 mg/kg) | 1,254±0,019** | 0,708±0,011** | 0,306±0,006** | 2,268±0,031** | 0,71±0,003** |
| | | | Limbic system | | |
| Control | 1,543±0,048 | 0,504±0,012 | 0,307±0,007 | 2,354±0,047 | 0,76±0,007 |
| Stress | 0,403±0,012* | 0,151±0,011* | 0,702±0,012* | 1,256±0,019* | 0,38±0,005* |
| Chlordiazepoxide (2 mg/kg) | 1,007±0,032** | 0,748±0,015** | 0,404±0,008** | 2,159±0,038** | 0,64±0,004** |
| Nikogamol (10 mg/kg) | 1,344±0,016** | 0,405±0,012** | 0,300±0,006** | 2,049±0,017** | 0,75±0,004** |
| Litonit (10 mg/kg) | 1,410±0,011** | 0,619±0,017** | 0,404±0,005** | 2,433±0,023** | 0,71±0,003** |
| | | | Medulla | | |
| Control | 1,595±0,047 | 0,602±0,009 | 0,509±0,009 | 2,706±0,051 | 0,70±0,006 |
| Stress | 1,202±0,021* | 0,402±0,012* | 0,302±0,006* | 1,906±0,019* | 0,74±0,005* |
| Chlordiazepoxide (2 mg/kg) | 1,212±0,028 | 0,703±0,011** | 0,495±0,010** | 2,400±0,037** | 0,65±0,004** |
| Nikogamol (10 mg/kg) | 1,318±0,041** | 0,704±0,014** | 0,253±0,005** | 2,275±0,049** | 0,73±0,004** |
| Litonit (10 mg/kg) | 1,357±0,016** | 0,967±0,019** | 0,221±0,006** | 2,485±0,024** | 0,73±0,003** |

Legend. *P < 0.05 compared with control; **P < 0.05 compared with stress. Number of observations in all experiments 10-15.

The aim of this investigation was to study the effect of certain nicotinic acid derivatives on brain energy metabolism.

## EXPERIMENTAL METHOD

Experiments were carried out on 520 male Wistar rats weighing 200-220 g and kept on the standard animal house diet. Highly emotional animals were selected for the experiments by preliminary testing [1]. On account of their typological characteristics and being placed in a conflict situation, the rats were in a state of anxiety neurosis [13]. Derivatives of nicotinic acid (vitamin PP), a natural metabolite of the animal, namely nikogamol and litonit, were used as correctors of the neurotic state. For comparison, the widely used benzodiazepine derivative chlordiazepoxide was used. The drugs were injected intraperitoneally in doses

of 10, 10, and 2 mg/kg, respectively (a 12-day course). Mitochondrial fractions of the sensomotor cortex, limbic system (hippocampus, hypothalamus, amygdala, and septal region) and medulla were isolated by differential centrifugation [10] in medium containing 0.32 M sucrose solution and 1 mM EDTA (pH 7.4). Purity of the isolated mitochondria was verified by testing succinate dehydrogenase activity [4] and by electron microscopy. Oxidative phosphorylation was determined manometrically [17]. The quantity of assimilated oxygen (ΔO) and of bound phosphorus (ΔP) was expressed in microatoms and calculated per 100 mg tissue per incubation time. Values of ΔP and ΔO thus obtained were used to calculate the P:O ratio, which reflects the degree of coupling of oxidation and phosphorylation [7]. Adenine nucleotides were determined in homogenates by an enzymic method [14], using reagents from Boehringer Mannheim, West Germany. The concentration of high-energy compounds was expressed in μmoles/g tissue and the adenylate charge in the form of a coefficient [11]. ATPase activity was measured by the increase in inorganic phosphorus in the incubation medium [15]. Samples for incubation contained, in a final volume of 1 ml (in mM): ATP (from Reanal, Hungary) 5, Tris-HCl 50, NaCl 100, KCl 20, $MgCl_2$ 5, ouabain glycoside (from Sigma, USA) 1; mitochondrial protein 100-120 μg; the pH of the incubation mixture was 7.4. Incubation continued for 15 min at 37°C. The reaction was stopped with 10% TCA. Protein was determined by Lowry's method [16]. Total ATPase activity was judged from the increase in $P_i$ in the presence of $Na^+$, $K^+$, and $Mg^{++}$ ions. $Mg^{++}$-dependent ATPase activity was taken to be the quantity of $P_i$ formed in medium containing ouabain glycoside as well as the above-mentioned ions, substrate, and enzyme. **$Na^+,K^+$-dependent ATPase activity** was given by the difference between total and $Mg^{++}$-ATPase activity. Enzyme activity was expressed in μmoles $P_i$/mg protein/h. The brain was removed in the cold; to determine adenine nucleotides it was frozen in liquid nitrogen. The results were subjected to statistical analysis on the Minsk-22m computer.

## EXPERIMENTAL RESULTS

Definite changes in the structure and function of certain organs and systems were found in animals in a state of neurosis. The main criteria for assessment of the animals' state were the formation of ulcers, erosions, and hemorrhages in the stomach, a decrease in the

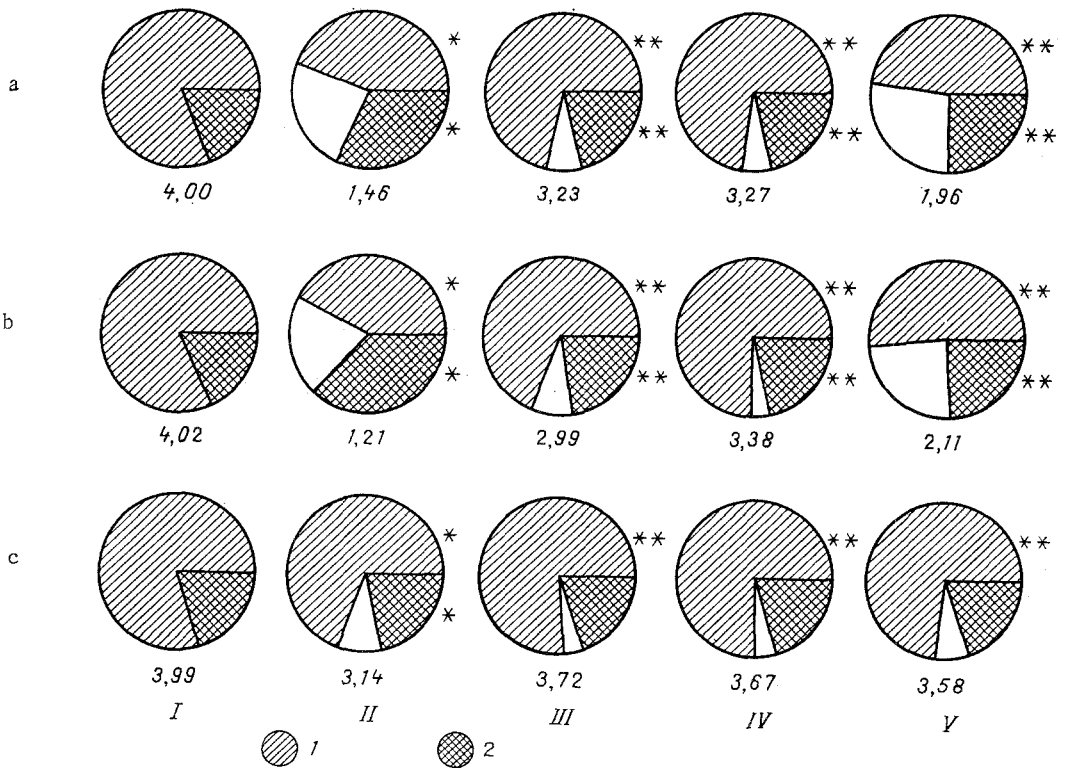


Fig. 2. Changes in ATPase activity of brain mitochondria during neurosis and its pharmacologic correction. a) Cortex; b) limbic system; c) medulla. 1) $Mg^{++}$-ATPase; 2) **$Na^+,K^+$-ATPase.** I) Control; II) stress; III) nikogamol; IV) litonit; V) chlordiazepoxide. Numbers indicate ratio between activities of $Mg^{++}$-ATPase and **$Na^+,K^+$**-ATPase. *P < 0.05 compared with control; **P < 0.05 compared with stress.

liver glycogen concentration, an increase in weight of the adrenals, and disturbance of mitochondrial structure. For instance, the weight of the rats' adrenals increased from 39.65 ± 3.15 to 54.52 ± 4.41 g ($P < 0.001$). In addition, clear disturbances of brain energy metabolism were found, and tissue respiration and phosphorylation were depressed and uncoupled. Phosphorylation processes were inhibited the most in a state of neurosis (by more than half). Inhibition of oxidative phosphorylation was observed primarily in the cortex, then in structures of the limbic system and, least of all, in the medulla (Fig. 1). Because of depression of oxidative phosphorylation, the main source of adenine nucleotide formation, the concentration of high-energy phosphates (ATP and ADP) was reduced. Whereas oxidative phosphorylation was inhibited virtually equally in the cortex and limbic system, the decrease in adenine nucleotide concentration was greater in the limbic system (by 3.8 times in the limbic system and 2.2 times in the cortex), where the lowest adenylate charge was observed (0.38 ± 0.005 compared with 0.77 ± 0.006 in the control; $P < 0.001$). Not only was the total concentration of high-energy compounds reduced, but there was also an unusual redistribution of the nucleotide pool: On the one hand, the ATP and ADP concentration was reduced, whereas, on the other hand, the AMP concentration was increased, with a reduction in Atkinson's coefficient (Table 1). It was considered no less important to study the principles governing utilization of energy of ATP under these conditions, for ATPase hydrolysis of ATP is the leading component in the utilization of energy of high-energy compounds and, at the same time, it maintains dynamic equilibrium of the nucleotide pool.

Activity of the ATPases showed sharp changes in the neurotic animals in all structures studied: $Mg^{++}$-ATPase activity was reduced and $Na^+,K^+$-ATPase activity increased. Whereas in the cortex and limbic system the decrease in $Mg^{++}$-ATPase activity was identical (Fig. 2), and amounted to 42.5 and 45.7%, respectively, it was almost four times less in the medulla (12.5%). A diametrically opposite picture, but maintaining the same principle, was observed with respect to $Na^+,K^+$-ATPase. Its activity increased significantly in all structures. Whereas for the limbic system and cortex the increase was significant and reached +81.2 and +57.6%, respectively, for the medulla it was only +11.3%. Considering current views on the role of $Na^+,K^+$-ATPase as a transport enzyme, it can be tentatively suggested that in neurosis its activity increases because of the need to intensify exchange processes between the mitochondria and cytoplasm. Meanwhile inhibition of $Mg^{++}$-ATPase activity can be regarded as evidence of a switch to a more economic level of utilization of energy substrates, if the inhibition of oxidative phosphorylation under these circumstances is taken into account. It follows from the results that keeping animals in a state of neurosis or a state of excessive catabolism disturbs not only the synthesis, but also the utilization of high-energy compounds. Another important factor is that the principal disturbances of brain energy metabolism develop in the limbic system and cortex, which is biochemical confirmation that these structures are involved in the formation of the psychoemotional response. The medulla, as a phylogenetically older structure, devoted to maintaining automatism of vitally important centers, shows the least degree of metabolic disadaptation. Disturbances of energy metabolism in it were minimal.

A prophylactic course of treatment with the drugs chosen for study showed that they have a marked antineurotic action. All drugs prevented ulcer formation to some degree or other, significantly reduced the number of erosions and hemorrhages, and normalized the glycogen level, mitochondrial structure, and weight of the adrenals. For instance, the weight of the adrenals was 45.21 ± 3.84 mg ($P < 0.05$) after chlordiazepoxide, 42.52 ± 5.07 mg ($P > 0.05$) after nikogamol, 41.34 ± 4.75 mg ($P > 0.05$) after litonit, compared with 39.65 ± 3.15 mg in the control (54.52 ± 4.41 mg in stress). However, the drugs acted differently on brain energy metabolism. Whereas chlordiazepoxide increased the concentration of high-energy compounds a little, at the same time it aggravated the effect of the neurosis on oxidative phosphorylation, and left ATPase activity virtually unchanged compared with the neurotic state. Nicotonic acid derivatives had a normalizing effect on brain energy metabolism. Oxidative phosphorylation was restored practically to its initial level (Fig. 1), the coupling coefficient was normalized, concentrations of adenine nucleotides were increased (Table 1), $Mg^{++}$-ATPase activity was raised, and $Na^+,K^+$-ATPase activity was depressed (Fig. 2).

The nicotinic acid derivatives studied thus not only have a marked depressant action, alleviating the course of the neurotic state in animals, but also have a definite influence on brain energy metabolism. Normalization of brain metabolism during development of neuroses is an important component of the mechanism of action of these substances and makes them promising candidates for use in practice.

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# ROLE OF THE LOCUS COERULEUS IN DEVELOPMENT OF CEREBROVASCULAR DISTURBANCES IN ACUTE MYOCARDIAL ISCHEMIA

L. G. Miller, Yu. I. Pivovarov, and G. N. Kryzhanovskii*

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KEY WORDS: locus coeruleus; acute cardiac ischemia; cerebral blood flow.

The development of cardiac arrhythmias in acute myocardial ischemia has been shown to be preceded by changes in electrical activity of the locus coeruleus (LC), and preliminary coagulation of LC under these conditions considerably reduces the intensity of the arrhythmia [4]. Disturbances of the cerebral hemodynamics also have been found in acute myocardial ischemia [3] and stimulation of LC is accompanied by slowing of the cerebral blood flow [6, 8-10].

In the investigation described below changes in the cerebral blood flow were studied during acute myocardial ischemia after coagulation of LC.

## EXPERIMENTAL METHOD

Experiments were carried out on 24 noninbred male rats weighing 200-240 g, anesthetized with sodium pentobarbital (25 mg/kg) and artificially ventilated (succinylcholine 0.2 mg/kg).

*Corresponding Member of the Academy of Medical Sciences of the USSR.

Department of Pharmacology and Department of Pathological Physiology, Irkutsk Medical Institute. Laboratory of General Pathology of the Nervous System, Institute of General Pathology and Pathological Physiology, Academy of Medical Sciences of the USSR, Moscow. Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 97, No. 4, pp. 400-401, April, 1984. Original article submitted June 10, 1983.

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