When the roles of these two factors are compared it must be remembered that disturbance of catecholamine synthesis under the influence of picolinic acid, a dopamine decarboxylase inhibitor, prevents damage to the heart but does not prevent the formation of gastric ulcers during stress [8, 9]. Meanwhile the development of ulcers and also of heart lesions is prevented by butyryl derivatives of picolinic acid penetrating into the brain. γ-Hydroxybutyric acid, which activates the inhibitory strionigral system in the brain, has a similar effect [6].

Factors with a central inhibitory action can thus prevent not only the disturbance of cardiac activity during stress, but also the formation of gastric ulcers. Adaptation to hypoxia does not have this effect, and it can therefore be concluded that this factor exerts its prophylactic effect through adaptive changes in the heart and in its regulatory apparatus.

LITERATURE CITED

1. F. Z. Meerson, The General Mechanism of Adaptation and Prophylaxis [in Russian], Moscow (1973).
2. F. Z. Meerson, L. M. Giber, G. I. Markovskaya, et al., Dokl. Akad. Nauk SSSR, 237, 1230 (1978).
3. F. Z. Meerson, M. G. Pshennikova, V. I. Kapel'ko, et al., Kardiologiya, No. 12, 50 (1975).
4. F. Z. Meerson, S. A. Radzievskii, L. M. Giber, et al., Dokl. Akad. Nauk SSSR, 237, 977 (1978).
5. M. G. Pshennikova and B. N. Manukhin, Dokl. Akad. Nauk SSSR, 198, 1474 (1975).
6. A. E. Uspenskii and V. P. Listvinova, Farmakol. Toksikol., No. 3, 266 (1972).
7. O. Desiderato, J. R. Mackinnon, and H. Hisson, J. Comp. Physiol. Psychol., 87, 208 (1974).
8. H. Hidaka, F. Hara, N. Hadada, et al., J. Pharmacol. Exp. Ther., 191, 384 (1974).
9. I. Gasuo, M. Chiyoko, and H. Masako, J. Pharmacol. Exp. Ther., 198, 589 (1976).

CHANGES IN THE NICOTINAMIDE NUCLEOTIDE CONTENT IN THE BRAIN AND MYOCARDIUM OF RATS EXPOSED TO FACTORS INDUCING NEUROGENIC DYSTROPHIES

E. A. Migas

UDC 616.8-009.85-092:577.152.1'133

The content of nicotinamide nucleotides in the brain and myocardium of rats was investigated during electrical stimulation of the animals and administration of toxic doses of noradrenalin. The level of total nicotinamide nucleotides and their oxidized forms was reduced but the content and rate of synthesis of nicotinamide nucleotide-phosphates were increased. The results point to a disturbance of oxidation–reduction processes and to an increase in the activity of the pentose pathway of carbohydrate utilization in the tissues in neurogenic dystrophies caused by extremal stimulation.

KEY WORDS: neurogenic dystrophies; nicotinamide nucleotides; energy metabolism; brain; heart.

Extremal stimulation causes a disturbance of nervous regulatory influences on metabolism in the tissues, with the consequent development of dystrophic changes in them. Disturbance of the functions of the sympathetic nervous system, a deficiency of catecholamines in the tissues, and marked inadequacy of energy metabolism are observed in such cases. The creatine phosphate level in the tissues falls, glycolysis is disturbed, the glycogen concentration is reduced, lactic acid accumulates, and oxidative phosphorylation is depressed [1, 4, 5, 7].

Laboratory of Experimental Pharmacology, Institute of Experimental Medicine, Academy of Medical Sciences of the USSR, Leningrad.

(Presented by Academician of the Academy of Medical Sciences of the USSR S. V. Anichkov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 86, No. 10, pp. 408-410, October, 1978. Original article submitted February 16, 1978.

0007-4888/78/8610-1290$07.50

Since energy metabolism is closely connected with the activity of oxidation-reduction processes involved in the oxidation of energy-rich compounds and the formation of high-energy phosphate bonds, it was decided to study these processes during the development of trophic disturbances caused by extremal stimulation.

The content of nicotinamide nucleotides, coenzymes of many of the dehydrogenases, including enzymes of aerobic and anaerobic carbohydrate conversion, and which constitute the first link in the chain of electron acceptors in the reactions of energy formation, was investigated after extremal stimulation. The level of nicotinamide nucleotides, the ratio between their oxidized (NAD, NADP) and reduced forms (NADH, NADPH), and also between nucleotide-phosphates and nucleotides are indices of metabolic activity in the tissues and largely reflect their functional state.

EXPERIMENTAL METHOD

Experiments were carried out on rats exposed to extremal stimulation: electrical stimulation for 3 h [3] and administration of toxic doses of noradrenalin (NA), which was injected intraperitoneally in a dose of 2.5 mg/kg. Tests in the laboratory showed that both these forms of stimulation caused neurogenic dystrophic lesions in the internal organs [1]. Tissue from the myocardium and brain was removed for investigation after stimulation for 3 h.

Oxidized and reduced forms of nicotinamide nucleotides were extracted separately [2, 8]. NAD was determined by an enzymic method based on its reduction by alcohol dehydrogenase; NADP was determined by Slater's method [12].

Besides the content of nicotinamide nucleotides, the activity of NAD-kinase was determined. This is an enzyme which synthesizes NADP from NAD, which is the sole source of formation of NADP in the tissues. NAD-kinase activity was determined in the brain tissue after electrical stimulation causing the most changes in the nucleotide-phosphate content. Activity of the soluble fraction of NAD-kinase obtained by centrifugation of brain homogenates in 0.02 M $KHCO_3$ at 16,000 rpm was investigated [2, 13].

EXPERIMENTAL RESULTS

The results showed that in response to extremal stimulation the level of oxidized forms of nucleotides was reduced in the tissues of the brain and myocardium compared with the control (Table 1), and in some series the level of total nicotinamide nucleotides also was reduced, evidence of inadequacy of oxidative processes during extremal stimulation. It can tentatively be suggested that this was connected with exhaustion of catecholamines, which exert a regulatory influence on the activity of oxygen consumption by the tissues, and, particular, with a fall in the NA level during electrical stimulation of the animals and through the action of toxic doses of exogenous NA [1, 5, 9]. A very important physiological function of NA is to regulate the oxygen consumption by the tissues, the activity of oxidative processes and of the enzymes participating in them, and also the intensity of oxidation-reduction processes [11, 14], through its action on α-adrenoreceptors [10].

Besides a decrease in the content of oxidized forms of nicotinamide nucleotides during extremal stimulation, the level of nucleotide-phosphates in the tissues was increased, mainly in the form of NADPH.

Determination of NAD-kinase activity revealed an increase in the intensity of NADP synthesis. NAD-kinase activity in the rats' brain after electrical stimulation for 3 h was significantly higher than in the control animals: 7.80 ± 0.80 and 4.65 ± 0.27 nmoles NADP/mg protein/h, respectively.

Since the level of nicotinamide nucleotides corresponds to activity of the dehydrogenases dependent on them, the accumulation of NADPH in the tissues and the increased synthesis of NADP may evidently indicate an increase in the activity of NADP-dependent dehydrogenases and, in particular, dehydrogenases of the glucose-monophosphate shunt. The role of this pathway of carbohydrate conversion is known to increase in the presence of an energy deficiency, for the affinity of glucose-6-phosphate dehydrogenase for glucose-6-phosphate is higher than that of the glycolytic enzymes. Investigations in the writer's laboratory have in fact shown that glucose-6-phosphate dehydrogenase activity is increased in neurogenic dystrophies of the myocardium induced by extremal stimulation [7].

TABLE 1. Content of Nicotinamide Nucleotides in the Myocardium and Brain of Rats (in μg/g wet weight; M ± m, n = 5) during Extremal Stimulation

Type of stimulation	Tissue	Groups	NAD	NADH	NAD+NADH	NADP	NADPH	NADP+ NADPH	NAD+NADP/ NADH+ NADPH
Electrical stimulation for 3h	Myocardium	Control	550,3±10,9	215,2±7,2	765,5±15,0	33,2±1,8	55,5±2,4	88,7±2,4	2,16
		Experimental	528,9±11,0	190,0±5,5*	718,9±12,1*	28,1±2,1	72,3±5,0*	100,4±6,3	2,07
	Brain	Control	265,0±5,0	157,7±2,1	422,7±4,7	30,1±3,6	29,3±1,0	59,4±3,5	1,58
		Experimental	254,4±3,8	167,0±5,4	421,4±5,3	35,2±4,0	36,9±1,2*	72,1±4,5*	1,42
Administration of toxic doses of NA	Myocardium	Control	549,8±4,5	235,0±4,0	784,8±3,5	38,1±3,1	52,5±4,2	90,6±5,6	2,04
		Experimental	479,1±16,0	284,0±9,2	763,1±17,5	27,9±2,3	54,0±4,7	81,9±3,9	1,50
	Brain	Control	250,7±8,0	144,5±2,0	395,2±7,8	28,8±2,7	30,8±1,7	58,8±2,8	1,60
		Experimental	192,0±3,6*	123,1±6,5*	315,1±7,1*	19,6±1,0*	41,6±1,7*	61,2±1,5	1,27

*P < 0.05 compared with control.

It is interesting to note that metabolic changes similar to those obtained in the present experiments have been found in tissues characterized by insufficiency of nervous control — in denervated and embryonic tissues, in which the activity of dehydrogenases of the glucose-monophosphate shunt and NAD-kinase is considerably increased [2, 6, 8].

It can be concluded on the basis of these results showing an increase in NADP synthesis, increased activity of glucose-6-phosphate dehydrogenase, and accumulation of NADPH that during extremal stimulation the activity of NADP-dependent dehydrogenase on the glucose-monophosphate pathway of carbohydrate conversion is increased, evidently as a result of disturbance of neurotrophic influences on tissue metabolism.

LITERATURE CITED

1. S. V. Anichkov, I. S. Zavodskaya, E. V. Moreva, et al., Neurogenic Dystrophies and Their Pharmacotherapy [in Russian], Leningrad (1969).
2. I. F. Belyaeva, I. D. Pevzner, and V. I. Telepneva, Zh. Évol. Biokhim. Fiziol., 8, 375 (1972).
3. O. N. Zabrodin, in: Annual Report of the Institute of Experimental Medicine, Academy of Medical Sciences of the USSR [in Russian], Vol. 7-8, Leningrad (1963), pp. 212-214.
4. I. S. Zavodskaya, E. V. Moreva, N. A. Novikova et al., Byull. Éksp. Biol. Med., No. 4, 61 (1974).
5. I. S. Zavodskaya, E. V. Moreva, N. I. Zaskal'ko, et al., Farmakol. Toksikol., No. 1, 44 (1975).
6. V. S. Il'in, A. M. Emel'yantseva, V. M. Pleskov, et al., Pat. Fiziol., No. 3, 3 (1972).
7. N. A. Novikova, Byull. Éksp. Biol. Med., No. 10, 1205 (1976).
8. V. I. Telepneva and R. Meshter, Biokhimiya, 34, 160 (1969).
9. S. V. Anichkov, I. S. Zavodskaya, and E. V. Moreva, Pharmacology, 5, 165 (1971).
10. S. Imai, T. Otorii, K. Takeda, et al., Jpn. J. Pharmacol., 26, 512 (1976).
11. J. Ribeilima, V. E. Wendt, H. Ramos, et al., Am. Heart J., 67, 672 (1964).
12. T. Slater, B. Sawyer, and U. Sträuli, Arch. Int. Physiol. Biochem., 72, 427 (1964).
13. T. Wang and N. Kaplaw, J. Biol. Chem., 206, 311 (1954).
14. J. Williamson and D. Jamieson, Molec. Pharmacol., 2, 191 (1966).