EFFECT OF TAURINE ON THE CYCLIC AMP AND GMP LEVELS IN THE RAT HEART DURING STRESS

L. S. Mal'chikova, N. V. Speranskaya, and E. P. Elizarova

UDC 616.45-001.1/.3-092.9-07: 616.12-008.939.633.2-074

Taurine had no effect on the cyclic nucleotide level in the heart of intact rats but sharply reduced the increase in cyclic AMP and cyclic GMP levels taking place during stress. The action of taurine on the cyclic GMP content in the heart was not exhibited after preliminary atropinization of the animals; its effect on cyclic AMP was greatly reduced after partial blockade of β-adrenoreceptors. It is suggested that taurine is a nonspecific regulator of the sensitivity of the myocardial cells to biologically active substances.

KEY WORDS: taurine; stress; cyclic AMP; cyclic GMP; receptor.

In several papers published recently a role is ascribed to taurine in the regulation of cardiac activity. Taurine has a therapeutic action in angina pectoris, ischemia, and cardiopathies [9,10], restores the pathological ECG spontaneously to normal [2], possesses inotropic properties, and abolishes fibrillation of the guinea pig heart caused by perfusion of the heart with medium deficient in K^+ [2].

However, the mechanism of the above-mentioned effects of taurine is by no means clear. It has been suggested that the physiological action of taurine on the heart is based on changes in the excitability of the heart muscle under the influence of this amino acid, through changes in permeability of the cell membrane to K^+ and Ca^{2+} [2-5]. Since taurine modifies the response of heart muscle to adrenalin and acetylcholine (ACh) [6], this suggests that it may have an effect on the receptors for these substances. Interaction of catecholamines and ACh with receptors is known to take place through the participation of adenylate- and guanylate-cyclase respectively, followed by changes in the levels of cyclic nucleotides in the cell.

Accordingly, in the investigation described below the effect of taurine on the cyclic AMP and cyclic GMP content in the rat heart was studied under conditions of stress.

EXPERIMENTAL METHOD

Experiments were carried out on 230 male Wistar rats weighing 250 g. The animals were compelled to swim in water at a temperature of 23-25°C for 15, 30, 45, and 60 min, after which they were rapidly immobilized. The heart was removed, washed with physiological saline, and frozen with Wohlenberger's forceps. The tissue was ground to powder in liquid nitrogen. Cyclic AMP and cyclic GMP were determined by a radioimmunologic method using kits from the Radiochemical Centre, Amersham, England. Taurine was injected intraperitoneally (0.4 g/kg) 10 min before swimming began. The β-adrenoblocker Obsidan (propranolol) in a dose of 2.5 mg/kg or the muscarinic (M) cholinergic blocking agent atropine, in a dose of 2 mg/kg, was injected into some of the animals 60 min before swimming began.

EXPERIMENTAL RESULTS

The content of cyclic AMP and cyclic GMP in the heart of the intact rats was 426 ± 35 and 43 ± 6.0 pmole/g wet weight of tissue respectively. An increase in the cyclic AMP concentration in the rat hearts was observed as early as 15 min after the beginning of swimming, a maximum was reached after 45 min, and the level remained high in rats which swam for 1 h (Fig. 1). The cyclic GMP concentration increased significantly only 45 min after the beginning of swimming, and it continued to rise 1 h after the beginning of the experiment.

Taurine had no effect on the content of cyclic nucleotides in the rats before swimming. However,

All-Union Cardiologic Scientific Center, Academy of Medical Sciences of the USSR. (Presented by Academician of the Academy of Medical Sciences of the USSR, E. I. Chazov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 87, No. 2, pp. 134-137, February, 1979. Original article submitted March 20, 1978.

 0007-4888/79/8702-0112$07.50

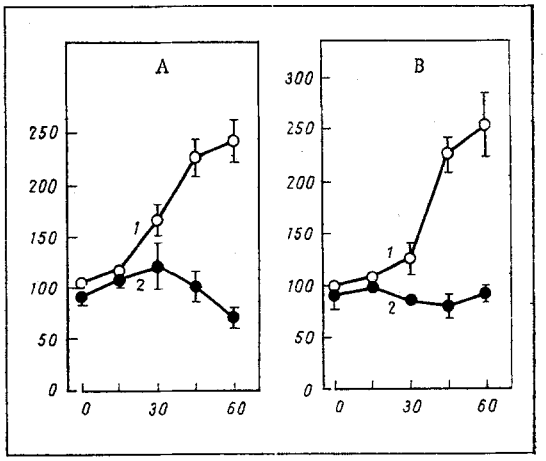

Fig. 1. Changes in cyclic AMP (A) and cyclic GMP (B) levels in rat heart during swimming. 1) Intact rats; 2) rats receiving taurine (0.4 g/kg) 10 min before swimming. Level of cyclic nucleotides in hearts of rats before swimming taken as 100%. Each point represents mean of 9-12 determinations. Here and in Figs. 2 and 3; abscissa, duration of swimming (in min); ordinate, level of cyclic nucleotides (in % of initial level).

injection of taurine 10 min before the beginning of swimming prevented the increase in the level of both cyclic nucleotides in the heart on account of stress. The cyclic AMP concentration after swimming for 60 min, in animals receiving taurine, was actually 20-25% below its initial level.

The decrease in the content of cyclic nucleotides in the heart during swimming in rats receiving an injection of taurine can be explained on the grounds that taurine changes the sensitivity of the cell membrane to adrenalin and ACh at the level of reception of these mediators.

This hypothesis was tested in rats compelled to swim (after previous injection of taurine or without taurine) after preliminary blockade of β-adrenergic and M-cholinergic receptors with Obsidan or atropine respectively. The experiments show that Obsidan lowered the initial cyclic AMP level in the heart of rats before swimming on average by 60%. Changes in the cyclic AMP concentration during swimming in the heart of the rats treated with Obsidan were considerably less marked than in the rats of the control group. Injection of taurine into these animals restored the cyclic AMP concentration during swimming to its previous level (Fig. 2a).

The cyclic GMP concentration after β-adrenoreceptor blockade in the rat heart at rest was 3 times higher than in the intact animals, so that their cyclic AMP/cyclic GMP ratio was approximately 1 (its mean value in intact rats was 10). The cyclic GMP level in these rats fell gradually during swimming. Taurine led to an increase in the cyclic GMP level 1 h after the beginning of swimming (Fig. 2b).

Injection of atropine into the intact animals led to a fall in the cyclic GMP and a rise in the cyclic AMP level in heart muscle. The ratio of cyclic AMP/cyclic GMP in these rats was 33 (Fig. 3). The cyclic GMP concentration was unchanged during swimming in the rats treated with atropine. Injection of taurine likewise had no effect. The cyclic AMP concentration in atropinized rats after swimming for 30, and, in particular, for 60 min was 4 and 8 times higher than the initial level respectively. Under the influence of taurine the cyclic AMP concentration in these rats fell sharply during swimming (Fig. 3).

Taurine was shown to have no effect on the cyclic nucleotide level in the heart of intact animals and to reduce their level sharply during stress. A decrease in cyclic GMP formation during cold stress has been observed in the brain under the influence of taurine [7]. The problem of the mechanism of these effects of taurine arises. During stress, taurine inhibits liberation of adrenalin from granules in the adrenals and lowers its blood concentration [8]. This may explain the observed decrease in the cyclic AMP concentration in the heart under the influence of taurine. However, the effect of taurine on the cyclic AMP concentration can also be examined at the receptor level. Taurine prevented the increase in cyclic AMP concentration in the heart during β-adrenoreceptor blockade which, at first glance, suggests absence of competition between taurine and

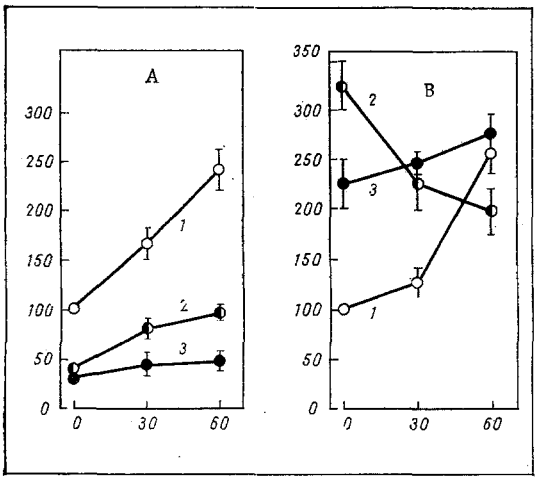

Fig. 2. Changes in cyclic AMP (A) and cyclic GMP (B) levels in rat heart after β-adrenoreceptor blockade. 1) Intact rats; 2) rats receiving intraperitoneal injection of Obsidan (2.5 mg/kg) 60 min before swimming; 3) rats receiving taurine and Obsidan before swimming. Each point represents mean of 6-9 determinations.

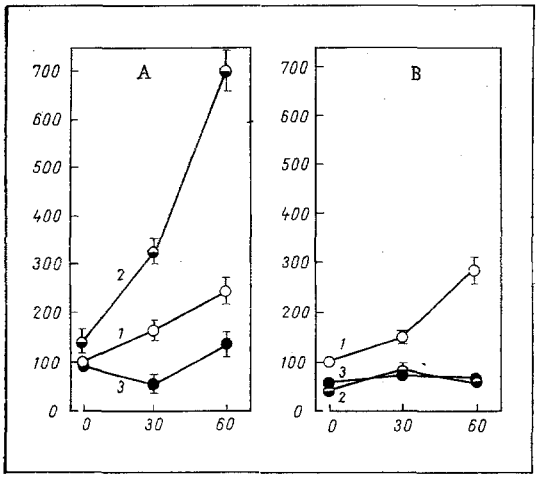

Fig. 3. Changes in cyclic AMP (A) and cyclic GMP (B) levels in rat heart during swimming after blockade of M-cholinergic receptors. 1) Intact rats; 2) rats receiving intraperitoneal injection of atropine (2 mg/kg) 60 min before swimming; 3) rats receiving taurine and atropine before swimming. Each point represents mean of 6-9 determinations.

adrenalin for the receptor. However, such a possibility cannot be ruled out, for Obsidan, in the concentrations used, could not completely block the adrenoreceptors, and a rise in the cyclic AMP level was observed during swimming.

Changes in the cyclic GMP concentration in the heart during stress did not take place in animals treated with atropine. No effect of taurine likewise was exhibited during swimming. The absence of any effect of taurine on the cyclic GMP concentration in the rat heart after M-cholinergic receptor blockade suggests competitive relationships between the cholinergic agents and taurine.

The results of these experiments do not allow any conclusions to be drawn regarding the molecular mechanism of the effect of taurine. Taurine is known to cause an increase in the permeability of membranes for Ca^{2+} in the myocardium [4]. A change in the Ca^{2+} concentration in the cell membranes in the presence of

taurine may be a factor controlling both the synthesis and catabolism of cyclic nucleotides [1]. Whatever its nature, the inhibitory action of taurine on the formation of cyclic AMP and cyclic GMP under conditions of stress can be regarded as a protective response of the body against overloading with adrenalin and ACh under extremal conditions.

LITERATURE CITED

1. M. N. Pertseva, Usp. Sovrem. Biol., 82, No. 1, 18 (1976).
2. E. I. Chazov, L. S. Malchikova, G. B. Asafov, et al., Circulat. Res., 35, 111 (1974).
3. J. Dietrich and J. Diacono, Life Sci., 10, 499 (1971).
4. P. Dolara, A. Agristi, A. Giotti, et al., Europ. J. Pharmacol., 24, 352 (1974).
5. P. Dolara, A. Agristi, A. Giotti, et al., Canad. J. Physiol. Pharmacol., 54, 529 (1976).
6. S. Fujimoto, H. Iwata, and Y. Yoneda, Jpn. J. Pharmacol., 26, 105 (1976).
7. A. Guidotti, G. Biggio, S. R. Naik, et al., in: Taurine, New York (1976), p. 243.
8. K. Kuriyama and K. Nakagave, in: Taurine, New York (1976), p. 335.
9. G. Nigro, J. Comia, and A. Loindice, Clin. Ter., 56, 347 (1971).
10. G. Nigro, F. Limongelle, and M. A. Giogliano, Clin. Ter., 56, 415 (1971).

CHANGES IN ACTIVE UPTAKE OF NORADRENALIN-^{14}C BY RAT BRAIN SYNAPTOSOMES DURING CONDITIONING

A. S. Bazyan and R. N. Glebov

UDC 612.825.1+08:612.822.1:577.175.522

Active uptake of noradrenalin-^{14}C (NA-^{14}C) by rat brain synaptosomes was shown to be inhibited by the action of ouabain (0.1 M) and during potassium depolarization. Defensive conditioning (DC) led to depression of active uptake of NA by synaptosomes. This effect may be connected both with changes in the state of the presynaptic membranes and with possible enhancement of the function of postsynaptic adrenergic receptors.

KEY WORDS: conditioning; active uptake of noradrenalin; rat brain synaptosomes.

An important step in the explanation of the mechanisms of formation and fixation of temporary connections is the study of functional changes in the synapses which may give rise to changes in their structure. A neurochemical index of a change in the efficacy of synaptic transmission is the highly specific active uptake of mediators by nerve endings [1, 9]. This index largely reflects presynaptic mechanisms of regulation of synaptic activity, namely the reassimilation of mediators, which is a method of inactivation of neurotransmitters and which probably plays an essential role in the realization of synaptic functions.

The basis for this investigation consisted of research which showed that, under certain conditions (stress [7, 8], electric shock [4]) the rate of uptake of biogenic amines by the corresponding nerve endings is changed, as experiments in vitro with labeled mediators have shown.

The object of this investigation was to study active uptake of noradrenalin-^{14}C (NA-^{14}C) by isolated nerve endings (synaptosomes) during defensive conditioning (DC).

EXPERIMENTAL METHOD

Experiments were carried out on 68 noninbred male albino rats weighing 180-200 g. Defensive conditioning to electric shock was produced in the animals in a shuttle chamber, in the form of bilateral avoidance with a 5-sec delay. The photic stimulus was light. Five correct responses to six presentations served as the criterion of DC.

Laboratory of Neurochemical Mechanisms of Conditioned Reflexes, Institute of Higher Nervous Activity and Neurophysiology, Academy of Sciences of the USSR. Laboratory of General Pathology of the Nervous System, Institute of General Pathology and Pathological Physiology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR A. M. Chernukh.)

Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 87, No. 2, pp. 137-139, February, 1979. Original article submitted May 23, 1978.