PURINERGIC ACTION OF ETHIMIZOLE

É. A. Migas

UDC 615.214.31.015.4:612.398.195

KEY WORDS: ethimizole; brain; adenosine receptors.

Recent investigations have shown the presence of so-called purinergic receptors in the CNS, activated by adenosine and adenine nucleotides, and for which caffeine and other methylxanthines are inhibitors [5, 9, 12]. The problem of whether these receptors perform a neuromediator or neuromodulating function has not been finally settled. It has, however, been shown that they are inhibitory for several brain regions — the cerebral cortex and hippocampus, whose activity is also depressed by ethimizole [1]. Considering the structural similarity of ethimizole with purine compounds, its inhibitory effect on central nervous structures, and its competitive action with caffeine on brain activity it can be tentatively suggested that ethimizole influences central adenosine receptors.

During excitation of adenosine-sensitive receptors and under the influence of adenosine the cAMP level in brain tissue has been shown to rise considerably as a a result of activation of adenylate cyclase, located on cell membranes [7, 11-13]. There is evidence of elevation of the ATP level in the tissues under the influence of adenosine [6].

The object of this investigation was to study the effect of ethimizole on the ATP and AMP levels and adenylate cyclase activity in brain tissue. Interaction of ethimizole with caffeine and adenosine also was investigated with respect to its effect on the ATP level and adenylate cyclase activity.

EXPERIMENTAL METHOD

Experiments were carried out on rats weighing 200 g, obtained from the "Rappolovo" nursery, Academy of Medical Sciences of the USSR, into which ethimizole was injected intraperitoneally in a dose of 20-25 mg/kg.

The cAMP level in brain tissue was investigated fluorometrically [2], adenylate cyclase activity was studied by a radioisotope method [8], and the ATP concentration by an enzymic method [10]. The rats were killed 20 min after injection of the preparation, by decapitation in order to determine enzyme activity, and by immersion in liquid oxygen to determine cAMP and ATP. Caffeine and adenosine were injected in doses equimolar with that of ethimizole, 2-3 min before injection of the latter.

EXPERIMENTAL RESULTS

The result showed that ethimizole more than doubles the cAMP concentration in brain tissue and considerably enhances adenylate cyclase activity (Fig. 1; Table 1). Caffeine was shown to have an inhibitory effect on the energy-forming influence of ethimizole (Table 1). A preliminary injection of caffeine abolished the rise in the ATP level in brain tissue induced by ethimizole. Adenosine potentiated this effect of ethimizole. The same relationship was found in the case of brain adenylate cyclase activity.

On the basis of these results and of electrophysiological data obtained previously in the Department of Pharmacology, Institute of Experimental Medicine, Academy of Medical Sciences of the USSR [1] it can be postulated that the action of ethimizole is connected with its effect on brain adenosine receptors.

Under the influence of ethimizole the intracellular cAMP level rises; this leads to activation of cAMP-dependent protein kinases which, as we know, intensify the most important

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Department of 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. N. Golikov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 94, No. 9, pp. 70-71, September, 1982. Original article submitted March 23, 1982.

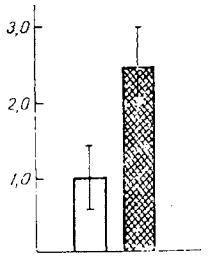

Fig. 1. Effect of ethimizole on cAMP level in rat brain. Unshaded columns — control, shaded columns — ethimizole. Ordinate, cAMP level (in nanomoles/g).

TABLE 1. Effect of Ethimizole, Caffeine, and Adenosine on ATP Concentration and Adenylate Cyclase Activity in Rat Brain (M ± m)

Experimental conditions	ATP concentration, μmoles/g	Adenylate cyclase activity, cpm/mg protein
Control	2,50±0,06 (*n*=10)	708±57 (*n*=5)
Ethimizole (20 mg/kg)	3,01±0,10* (*n*=10)	1102±106* (*n*=5)
Caffeine 20 mg/kg + ethimizole 20 mg/kg	2,56±0,07 (*n*=7)	885±64 (*n*=5)
Caffeine 20 mg/kg	2,69±0,07 (*n*=7)	—
Adenosine 30 mg/kg + ethimizole 20 mg/kg	3,17±0,11* (*n*=7)	1476±117* (*n*=5)

Legend. *P < 0.05 compared with control. Number of determinations in parentheses.

metabolic reactions in neurons. cAMP is known to increase neuronal activity, to promote acetylcholine release from nerve endings, and to increase the velocity of the axoplasmic flow of synaptic vesticles and neurosecretory granules [3]. cAMP participates in the secretion of neurohumoral agents, including neurosecretion which stimulate pituitary activity [4].

It can be tentatively suggested that the action of ethimizole on central nervous structures is based on a dual mechanism of its activity, the directions of which are opposite. As a result of this, ethimizole has a biphasic effect on several brain structures, a short-term depressive effect being followed by a longer lasting excitatory action [1].

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