Journal of Biological Sciences 6 (6): 968-977, 2006
ISSN 1727-3048

Effect of Drugs from the Class of Cardiac on the Na^+, K^+-ATPase Activity

Z.I.A. AL-Fifi
Department of Biological Sciences, Faculty of Science, King Abdulaziz University,
P.O. Box 80094, Jeddah 21589, Saudi Arabia

Abstract: The effect of drugs from the class of cardiac (methyldigoxin, verapamil, propranolol), antiepileptic (carbamazepine), sedative (diazepam) and antihistaminic (promethazine) drugs on Na^+, K^+-ATPase activity of plasma membranes in rat brain synaptosomes was studied. Methyldigoxin in concentration of 0.1 mmol L^{-1} inhibits enzyme activity by 80%. Verapamil, propranolol and promethazine in concentrations of 20, 20 and 2 mmol L^{-1}, respectively, inhibit entirely this ATPase activity. Carbamazepine and diazepam in concentrations of 0.02-60 mmol L^{-1} have no effect on the activity of this enzyme. According to drugs concentrations that inhibit 50% of enzyme activity (IC_{50}), the potency order of drugs was: methyldigoxin >> promethazine > verapamil ≥ propranolol. From inhibition of commercially available purified Na^+, K^+-ATPase isolated from porcine cerebral cortex in the presence of chosen drugs, as well as from the kinetic studies on synaptosomal plasma membranes, we may concluded that the drugs inhibit enzyme activity, in partly by acting directly on the enzyme protein. Propranolol, verapamil and promethazine inhibitions were in an uncompetitive manner. The results suggest that these three drugs may contribute to neurological dysfunction and point out to the necessity to take into consideration the side effects of the investigated drugs during the treatment of various pathological conditions.

Key words: Na^+, K^+-ATPase, synaptosomes, verapamil, propranolol, promethazine

INTRODUCTION

Na^+, K^+-ATPase, supporting the ionic homeostasis of the cell, is under control of Na^+, K^+, Mg^{2+} and ATP. Due to significant importance of the Na^+, K^+-ATPase in the maintenance of neuronal resting membrane potentials and propagation of neuronal impulses, the malfunction of this enzyme has been associated with neuronal hyper excitability, cellular depolarization and swelling (Lees, 1991). In numerous tissues, the activities of Na^+, K^+-ATPase may be influenced by different endogenous modulators (Rodrigez *et al*., 1995; Balzan *et al*., 2000; Ewart and Klip, 1995). Na^+, K^+-ATPase activity is decreased by toxic actions of normal neurotransmitters such as glutamate (Brines *et al*., 1995), which is the cause of cell injury and death of neurons, the basic events of cerebral ischemia in epilepsy and in various neurodegenerative disorders (Wyse *et al*., 2000; Grisar, 1984; Lees, 1993). Catecholamines induce marked stimulation of Na^+, K^+-ATPase activity by stimulation of β2-adrenoceptors, leading to hyperpolarization of the cell membrane (Clausen and Flatman, 1977).

With regard to the importance of this enzyme for the proper functioning of cells and tissues and in the induction of cytotoxicity, especially in nerve cells, the present study was undertaken in order to examine the effects of particular drugs on Na^+, K^+-ATPase. The effect of drugs from the class of cardiac (methyldigoxin, verapamil, propranolol), antiepileptic (carbamazepine), sedative (diazepam) and antihistaminic (promethazine) drugs on Na^+, K^+-ATPase in synaptic plasma membranes prepared from the whole rat brain were investigated. Known pharmacological effects of these drugs are not detected concerning the synaptosomal Na^+, K^+-ATPase activity. Methyldigoxin was known to inhibit Na^+, K^+-ATPase in various tissues but it was included in our experiments with the purpose to compare its efects with effects of other two anthyarrhitmic drugs. For propranolol, there is litle evidence while for verapamil and promethasine there is no information of their effects on brain Na^+, K^+-ATPase. Carbamazepine and diazepam were examined because their effect on synaptosomal Ca-ATPase, sodium channels and ATPase were priviously observed, but there is no data of their Na^+, K^+-ATPase activity modulation. Also, the effects of the chosen dugs on the commercial Na^+, K^+-ATPase from porcine brain were examined with the aim to evaluate if the effects of these drugs may be directly on the enzyme protein. In addition, extensive kinetic studies were undertaken to determine the nature of the drugs action.