

Kalsi K, R Smolenski, M Yacoub. Effects of nucleoside transport inhibitors and adenine/ribose supply on ATP concentration and adenosine production in cardiac myocytes. *Moll Cell Biochem* 1998;180(1-2):193-199.

Adenosine plays an important role in protection of the heart before, during and after ischemia. Nucleoside transport inhibitors (NTI) increase adenosine concentration without inducing ischemia by preventing its uptake and metabolism in cardiac cells. However, prolonged effects of nucleoside transport inhibitors on adenosine and nucleotide metabolism and its combined effect with nucleotide precursors has not been established in cardiomyocytes. The aim of this study was to investigate the effect of two nucleoside transport inhibitors, dipyridamole (DIPY) and nitrobenzylthioinosine (NBTI) alone or combined with adenine and ribose on adenosine production and ATP content in cardiomyocytes. Rat cardiomyocytes were isolated using collagenase perfusion technique. Isolated cell suspensions were incubated for up to 480 min with different substrates and inhibitors as follows: (1) control; (2) 100 microM adenine and 2.5 mM ribose; (3) 10 microM DIPY; (4) 1 microM NBTI; (5) DIPY, adenine and ribose and (6) NBTI, adenine and ribose. Five microM EHNA (erythro-9(2-hydroxy-3-nonyl)adenine, an inhibitor of adenosine deaminase) was added to all incubations. After incubation, extracts of myocyte suspension were analysed by HPLC for adenine nucleotides and metabolite concentrations. ATP content decreased in cardiomyocytes after 8 h of incubation with DIPY, while no change was observed with NBTI or without inhibitors. Adenosine concentration increased with both DIPY and NBTI. In the presence of adenine and ribose an elevation in ATP concentration was observed, but no significant change in adenosine content. In the presence of DIPY or NBTI together with adenine and ribose, an enhancement in cardiomyocyte ATP concentration was observed together with an increase in adenosine content. This increase in adenosine production was especially prominent with DIPY. In conclusion, dipyridamole causes a decrease in ATP concentration in isolated cardiomyocytes by mechanisms other than nucleoside transport inhibition. Addition of adenine/ribose with dipyridamole prevents the depletion of ATP. Combination of adenine/ribose with nucleoside transport inhibitors may also further enhance adenosine concentration and thus, could be more effective as pharmacological agents for treatment.