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Adenosine kinase and the control of adenosine concentration in the heart

The qualitative approach in metabolic control is to study the properties of enzymes that catalyse non-equilibrium reactions in order to identify possible external regulators of this enzyme and then test the resulting hypothesis of control in the intact system (see Newsholme & Leech, 1983). Adenosine kinase catalyses a non-equilibrium reaction in all tissues investigated, and if both 5′-nucleotidase and adenosine kinase are simultaneously catalytically active a substrate ('futile') cycle between AMP and adenosine will occur and this might be of considerable importance in control of the adenosine concentration in various tissues including the heart (Arch & Newsholme, 1978). As part of a systematic study of the enzymes involved in the control of adenosine concentration, the properties of the kinase were investigated and a hypothesis for control of the adenosine concentration put forward (Fisher & Newsholme, 1984). The work of Newby *et al.* (1983) tested this hypothesis and, as pointed out by Newby (1984), the results provided little or no support for the hypothesis. This suggests either that adenosine kinase plays no significant role in control of the adenosine concentration (Newby, 1984) or that there are other as yet undiscovered properties of this enzyme that are important in control. We wish to put forward a speculative proposal.

The improvement in sensitivity for controlling fluxes or concentrations of metabolites via a substrate cycle depends upon the ratio, cycling rate/flux (Newsholme & Crabtree, 1976; Newsholme *et al.*, 1984). Consequently the sensitivity provided by such cycles is variable depending on the cycling rate. Recently it has been shown that catecholamines can dramatically increase the cycling rate in the triacylglycerol/fatty acid cycle (Brooks *et al.*, 1983) and the fructose/fructose 6-phosphate cycle (Challiss *et al.*, 1984). Such increases in cycling might be achieved by covalent modification of one or both enzymes in the cycle. Hence it is suggested that catecholamines or other hormones increase the activity of adenosine kinase (and possibly 5′-nucleotidase) which increases the cycling rate between AMP and adenosine in such a way that the properties reported by Fisher & Newsholme (1984) would *now* be important in the regulation of the adenosine concentration. Thus, we expect that the rate of cycling would increase dramatically in heart when an increase in heart work was anticipated so that a sensitive mechanism for control of adenosine concentration would be available to adjust precisely coronary flow to increased metabolic demand by the heart.

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