Table 1 Enzyme activities in pancreatic homogenates from control and penicillamine treated rats. The values indicated are the mean ± s.e. mean (no. of animals). For all enzymes the control and treated activities are significantly different, $P \leqslant 0.005$ (Mann-Whitney U test)

Enzyme	*Control*	*Penicillamine treated*
Amylase (i.u./mg DNA)	35,258.6 ± 5361.7 (7)	118.9 ± 43.6 (23)
Succinic Dehydrogenase (μmoles Formazan min^{-1} mg DNA^{-1})	162.4 ± 32.5 (7)	415.3 ± 60.4 (23)
ATPases (μmoles Pi min^{-1} mg DNA^{-1})		
(1) Mg^{2+}-ATPase	19.3 ± 2.2 (7)	51.5 ± 7.7 (23)
(2) Ca^{2+}-ATPase	19.5 ± 2.4 (7)	62.2 ± 8.5 (23)

It is concluded that this preparation may prove a useful model for the study of pancreatic duct cells.

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Inhibition of rabbit muscle pyruvate kinase by lithium

M.J. O'BRIEN, C.N. ALLIN, N.J. BIRCH & R.P. HULLIN

Department of Biochemistry, University of Leeds

Lithium is of importance in the prophylactic treatment of manic-depressive psychoses but its exact mode of action is not known. It has been suggested that an important aspect of its action is via interaction with magnesium dependent enzymes (Birch, 1974). Lithium was originally shown to inhibit pyruvate kinase by Kachmar & Boyer (1953) though the level of lithium used was very high (100 mM). A preliminary report of lithium's action on a number of magnesium dependent enzymes has been made (Birch, Hullin, Inie & Leaf, 1974).

The present work was undertaken to provide a detailed investigation of the inhibition of pyruvate kinase by lithium. The interaction of lithium with all the substrates of the enzyme was examined and the results indicate that lithium was competitive with respect to ADP binding to the enzyme and non-competitive with respect to all other substrates. Under the normal assay conditions (85 mM Tris.HCl buffer, pH 7.5, 0.5 mM phosphoenolpyruvate, 10 mM magnesium chloride, 5 mM ADP, 20 mM potassium chloride, 0.25 mM NADH and excess lactate dehydrogenase) 10 mM lithium produced a 16–24% inhibition of the maximum pyruvate kinase activity. This is a lower level of inhibition than indicated by the previous preliminary study (Birch *et al.*, 1974) but is still at a significant level. At the intracellular ADP concentrations of approximately 1.2 mM the level of inhibition is markedly increased. Further work to discriminate between a specific lithium, general ion, or ionic strength phenomena showed that it was not a general ion nor ionic strength effect but that inhibition was also found with calcium and sodium, the order of inhibition being calcium > lithium > sodium. Kinetic investigation showed that the calcium inhibition was of a similar type to lithium, i.e. competitive to ADP binding. However calcium levels unlike lithium levels are rigidly controlled by the body and so the inhibition of pyruvate kinase by calcium is unlikely to be of physiological significance.

The prophylactic dose of lithium gives a plasma lithium level of 0.6–1.4 mM (Hullin, McDonald & Allsopp, 1972) and at this level the inhibition of pyruvate kinase is insignificant. There is still the possibility however of accumulation of lithium in certain body tissues. Should the level be raised to 4 or 5 mM the level of inhibition would be significant especially at the intracellular ADP level. Whether these conditions of 4–5 mM lithium are likely is open to question.

There might be other magnesium dependent enzymes which are more sensitive to lithium levels than pyruvate kinase and we are looking at this possibility.

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Tissue variability and some properties of the accumulation of [^{3}H]-corticosterone by isolated organs

A. GIBSON & CAROLINE V. STREET

Department of Pharmacology, Chelsea College, University of London, SW3 6LX

Administration of corticosteroid hormones enhances the responsiveness of a number of tissues to agonist drugs and to nerve stimulation (Brodie, Davies, Hynie, Krishna & Weiss, 1966; Gibson, Pollock & Spence, 1976). This supersensitivity may be due to a redistribution of Na^+ ions within the tissue, probably as a result of hormone-induced enzyme synthesis (Gibson & Pollock, 1976; Scott & Sapirstein, 1975). The first step in the action of corticosteroids on a target organ is entry of the hormone into the cell (Gorski & Gannon, 1976). However, the entry process is poorly defined, and differences in steroid uptake by various tissues have been reported (Jensen & Jacobson, 1960). We therefore began an investigation of the action of corticosteroids on cellular reponsiveness by observing the accumulation of [^{3}H]-corticosterone in various isolated tissues.

Animals were killed by stunning and exsanguination. The tissues were rapidly dissected and incubated at 37°C in Krebs bicarbonate solution containing [^{3}H]-corticosterone (70 nM; 112 Ci/mmole; Amersham). The medium was gassed with 95% O_2 5% CO_2. At various time intervals tissues were removed, blotted, weighed and digested in 1 ml potassium hydroxide (0.5 M; 60°C). The radioactivity in a 0.1 ml aliquot of digestant was then measured using a toluene-Triton scintillation fluid.

Initially accumulation of [^{3}H]-corticosterone was observed in the rat anococcygeus muscle. In this tissue, equilibrium was reached within 30 min, and the tissue/medium ratio after 2 h was 2.2 ± 0.07 ($n=6$). However, there was a marked tissue variability in accumulation, the tissue/medium ratios for other tissues following a 2 h incubation being: rat heart (2.5 ± 0.2); mouse heart (3.7 ± 0.05); rabbit vas deferens (3.4 ± 0.3); mouse vas deferens (7.4 ± 0.3); rat pituitary (5.6 ± 0.3); rat hypothalamus (2.6 ± 0.09). The highest tissue/medium ratio was achieved in the mouse vas deferens and this tissue was used to study some further characteristics of the accumulation process.

Dichloromethane extraction of incubated tissues suggested that 96% of extractable radioactivity was unchanged corticosterone. The accumulated steroid was well retained by the vas, the time of washout being 3 times that of accumulation. The accumulation was temperature sensitive being reduced by 32% at 20°C and by 51% at 4°C. Reduction of the Na^+ content of the medium to 25 mM enhanced accumulation. Rather surprisingly, accumulation was also enhanced by ouabain (10^{-4} M). Preliminary experiments suggest that part of the accumulation is mediated by a specific process since it could be reduced by excess corticosterone (10^{-4} M) but not by hydrocortisone (10^{-4} M).

In conclusion, the accumulation of [^{3}H]-corticosterone exhibited a marked tissue and species variation. Indeed, in the case of cardiac and smooth muscle this variation exhibited a marked similarity to that described for extraneuronal accumulation of catecholamines (Gillespie & Muir, 1970). The mechanisms responsible for the accumulation and its relation to cellular responsiveness is under investigation.

CVS is an M.R.C. Student

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