Glucose and the Survival and Recovery of the Anoxic Myocardium

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The mammalian heart is particularly sensitive to periods of O₂ deprivation. Under hypoxic stress, induced either clinically or pathologically, the survival and subsequent recovery of the heart depends on the ability of the myocardium to maintain its biochemical and morphological integrity. An isolated perfused working rat heart preparation (Chain *et al.*, 1969) has been used to investigate the biochemical changes associated with complete anoxia and post-reoxygenation recovery, and also the role played by glucose, K⁺ and insulin in aiding the survival and recovery of the anoxic myocardium.

Within 30s from the onset of anoxia the heart is unable to perform any external work, the creatine phosphate content of the heart falls to less than 50% of its aerobic control value, the ATP content falls less rapidly but after 20min is decreased to less than 10%, the P_i content increases accordingly and there is a great increase in lactate production. Under certain circumstances, even after prolonged anoxia (as long as 30min), after reoxygenation the heart is able to recover almost complete mechanical activity [as monitored by aortic output against a 0.13 MN/m² (100cmH₂O) pressure head]. Recovery is paralleled by a very rapid increase in the creatine phosphate content, a progressive rise in ATP content, a corresponding fall in ADP and AMP contents and a sharp fall in lactate production. It was found that the presence of glucose and insulin in the perfusion fluid during anoxia was essential for complete recovery, and that a high concentration of K⁺ increased not only the rate of recovery but also the final extent of recovery. Glucose could not be replaced by pyruvate or lactate, but could be replaced by high concentrations of glucose 1-phosphate (Beloff-Chain *et al.*, 1953). The ability of the heart to recover is proportional to the myocardial ATP content at the time of reoxygenation. The presence of glucose (11.1mM) during the anoxic period results in a striking diminution in the rate of decrease of ATP and creatine phosphate contents. It is proposed that glucose aids in the survival and recovery of the anoxic heart by serving as an exogenous source of substrate for anaerobic glycolysis, and thereby facilitating the maintenance of higher ATP and creatine phosphate contents, which in turn promote survival and recovery of the heart.

This work was carried out with the aid of a grant from the British Heart Foundation. The skilled assistance of Mr. A. Mullins is gratefully acknowledged.

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Formation of Glucose from Glucose 6-Phosphate by Rat Brain Slices

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During investigations into the metabolism of glucose 6-phosphate by rat cerebral-cortex slices it became clear that one of the metabolites formed was glucose (Balliano *et al.*, 1969; Dodd *et al.*, 1971). Since glucose is much preferred to glucose 6-phosphate as a substrate for brain slices, it was decided to investigate the extent of glucose formation from glucose 6-phosphate *in vitro*, as this could be an obligatory first stage in its metabolism.

Rat cerebral-cortex slices were maintained for 1h at 38°C in bicarbonate- or tris-buffered saline in the presence of 25mM-glucose 6-phosphate as substrate, 0.25% (w/v) inulin and 1μCi of [carboxy-¹⁴C]inulin. Perchloric acid extracts of tissue and medium were prepared and ¹⁴C radioactivity and glucose determined. The tissue/medium ratio of glucose was approx. 10 times the tissue/medium ratio of ¹⁴C, indicating the presence of intracellular glucose. In contrast, no evidence for the existence of an intracellular glucose pool was found with 10mM-glucose substrate. Evidence for such a pool was found with 25mM-fructose 6-phosphate or 10mM-fructose as substrate, but not with 25mM-fructose 1,6-diphosphate or 25mM-glycerol 2-phosphate as substrate, nor when no substrate was present.

When O₂ uptake and lactate formation were inhibited with CN⁻ and iodoacetate, glucose formation from glucose 6-phosphate continued: approx. 12μmol of glucose/g initial wt. and 15μmol of P_i/g initial wt. accumulated in 1h in the medium from brain slices incubated at 38°C with 25mM-glucose 6-phosphate in tris-buffered saline (a similar amount of P_i was also formed in the absence of the poisons). This apparent glucose 6-phosphatase activity in the medium was inhibited by HCO₃⁻ and P_i ions, but not by glucose. A number of phosphate esters (*p*-nitrophenyl phosphate, glycerol 2-phosphate, fructose 6-phosphate, glucose 1-phosphate) were lysed under similar conditions to those used for glucose 6-phosphate.

An increase in K⁺ concentration in the medium to 55mM, which caused an increase in slice hourly