Journal of Molecular and Cellular Cardiology (1980) **12**, 225–227

A Protective Effect of Thiopentone on Hypoxic Heart Muscle

Thiopentone and other barbiturates have been shown to protect the brain against hypoxic or ischaemic damage [*3*, *4*]. Dose regimes varying from 30 to 90 $mg \cdot kg^{-1}$ body weight have been suggested [*1*, *6*]. This is grossly in excess of the dosage used for induction of anaesthesia which is in the range of 3 to 5 $mg \cdot kg^{-1}$ body weight. These facts have led to the introduction of controlled trials of thiopentone in cerebral protection clinically as part of the burgeoning field of brain resuscitation [*6*]. The amount of thiopentone that may be used is limited by the cardiovascular effects of the drug, such as a decrease in arterial blood pressure and cardiac output [*2*]. As the usage of barbituarates for brain protection has been employed clinically by one of the authors (D. Sinclair) during cardiopulmonary by-pass procedures, it was decided to investigate the possible concomitant protective effects of thiopentone on the heart.

Isolated rat hearts were perfused at 37°C according to Langendorff at a pressure of 10.0 kPa (75 mmHg). The standard perfusion medium [*5*] was equilibrated with 95% O_2–5% CO_2 and contained glucose (11 $mmol \cdot litre^{-1}$). For hypoxic perfusion the medium was equilibrated with 95% N_2–5% CO_2 and contained mannitol (11 $mmol \cdot litre^{-1}$) instead of glucose. After a 15 min stabilization period, the hearts were perfused for 40 min with the hypoxic medium. Subsequently the hearts were reoxygenated for 30 min. When required, thiopentone (50 or 200 $mg \cdot litre^{-1}$) was added to the hypoxic medium. Samples of the effluent medium were collected and analysed for creatine kinase (CK) activity, using a Vitatron Automatic Kinetic Enzyme System (AKES) and a Boehringer CK NAC-activated kit. Enzyme activity was expressed in IU released $\cdot min^{-1} \cdot g^{-1}$ dry heart tissue. Results were analysed for significance by Student's t test, taking $P = 0.05$ as the limit of significance.

During the 15 min stabilization period the hearts did not release measurable amounts of CK. The subsequent period of hypoxic glucose-free perfusion caused a slow CK release which amounted to 2.11 ± 0.33 IU $\cdot min^{-1} \cdot g^{-1}$ dry weight after 40 min of hypoxia (Figure 1). Reoxygenation of the hearts resulted in an exacerbation of the CK release, with a peak value of 38.0 ± 5.8 IU $\cdot min^{-1} \cdot g^{-1}$. When 50 $mg \cdot litre^{-1}$ thiopentone was added to the hypoxic medium, the CK release was reduced both during hypoxia (0.82 ± 0.08 IU $\cdot min^{-1} \cdot g^{-1}$ after 40 min of hypoxia; $P < 0.05$) and during the reoxygenation period (peak value

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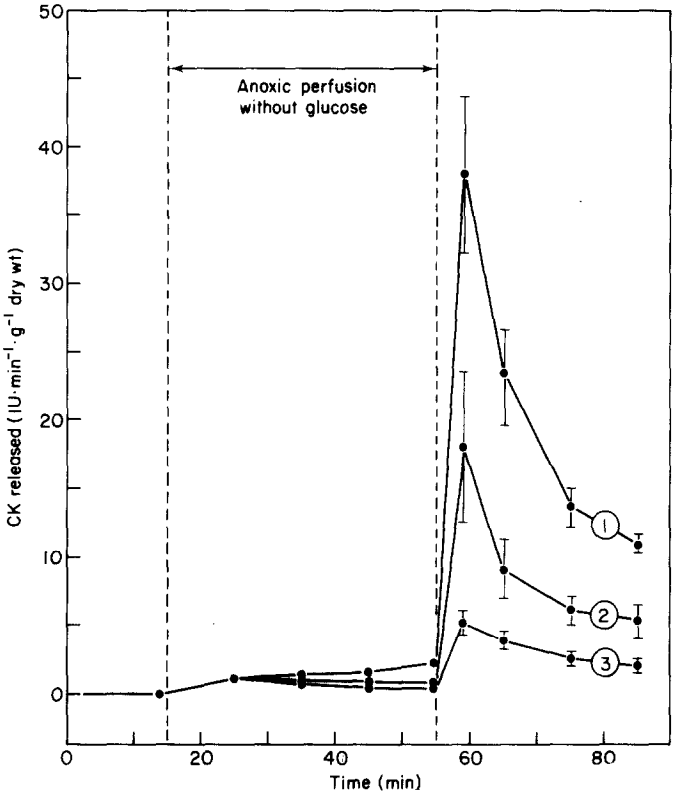

FIGURE 1. Effect of hypoxic glucose-free perfusion and subsequent reoxygenation, on the release of CK (IU·min^{-1}·g^{-1} dry wt) from isolated rat heart. (1), −thiopentone; (2), +50 mg·litre^{-1} thiopentone; (3), +200 mg·litre^{-1} thiopentone. Values are given as mean ± S.E.M. ($n = 6$).

18.0 ± 5.5 IU·min^{-1}·g^{-1}; $P < 0.05$). Inclusion of 200 mg·litre^{-1} thiopentone in the hypoxic medium resulted in a further reduction of the CK release from both the hypoxic and reoxygenated hearts. The reoxygenation peak of the 200 mg·litre^{-1} series (5.1 ± 0.7 IU·min^{-1}·g^{-1}) was significantly lower than that of the control and the 50 mg·litre^{-1} series ($P < 0.001$ and $P < 0.05$, respectively).

These results can be interpreted to mean that thiopentone can, at least under certain circumstances, protect heart muscle against some of the deleterious effects of hypoxia and in so doing can decrease the reoxygenation damage. Additional studies are needed to establish the basis of this protection. It is possible that the protective effect may be associated with the drug's negative inotropy which would decrease the consumption of myocardial high-energy phosphate stores during the period immediately following the onset of hypoxic perfusion. It is also possible

that thiopentone exerts a protective effect on the cell membrane, rendering it less susceptible to damage.

Acknowledgements

We thank Dr A. N. E. Zimmerman and Professor Dr F. L. Meijler for supporting this study.

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