responds to a cooperative binding process, whereas a much less significant effect is determined by a competitive interaction.

It is significant that widely different conformations, such as those observed for BSA at two pH values (2.2 and 6.8 respectively)[22] do not necessarily imply a proportional difference in binding and transport capacities of the protein for the antibiotic[11].

Furthermore, the volume decrease produced by the interaction of SDS with negatively charged BSA[23], which occurs at premicellar detergent concentrations, suggests that, along with binding processes, changes in the geometry of the biomebrane might be significant in determining the transport rate of the permeants.

Résumé. L'étude de l'influence de concentrations prémicellaires des tensioactifs sur l'interaction BSA-CAF permet de conclure qu'il s'agit d'un mécanisme cooperatif suivant le modèle allosterique proposé par MONOD, WYMAN et CHANGEUX[19]. Ce mécanisme représente une possible explication de l'influence des tensioactifs sur l'absorption des médicaments.

F. ALHAIQUE, M. MARCHETTI, F. M. RICCIERI and ELEONORA SANTUCCI[24]

Cattedra di Tecnica Farmaceutica, Istituto di Chimica Farmaceutica dell'Università di Roma, Roma (Italy), 8 August 1974.

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Contractile Response of Halothane-Depressed Isolated Atria to Various Substrates

In our previous report[1] dealing with the mechanism of cardiac depressant action of inhalation anesthetic halothane, it has been demonstrated that: 1. approximately 6 mg/100 ml halothane is required to maintain 50% depression of the force of contraction of isolated rat atria in Krebes-Ringer bicarbonate glucose medium; 2. pyruvate partially restores the contractility of halothane-depressed atria, but has no effect on normal atria. From these findings we concluded that the cardiac depressant action of halothane on rat atria is a manifestation of inhibition of glucose uptake or utilization. The present studies were undertaken to observe the effect of other substrates on halothane-depressed atria in order to substantiate our conclusions. As with the case of pyruvate, lactate and acetate also partially restored the force of contraction of halothane-depressed atria. These data are consistent with the hypothesis that halothane inhibits glucose uptake or utilization in the glycolytic cycle of the myocardium.

Method. Atria from decapitated rats were used as previously described[1,2]. Halothane was administered into the medium by means of anaesthesia[3]. The halothane concentration in the medium was determined at 10 to 30 min intervals with a gas chromatograph throughout the experimental period[3].

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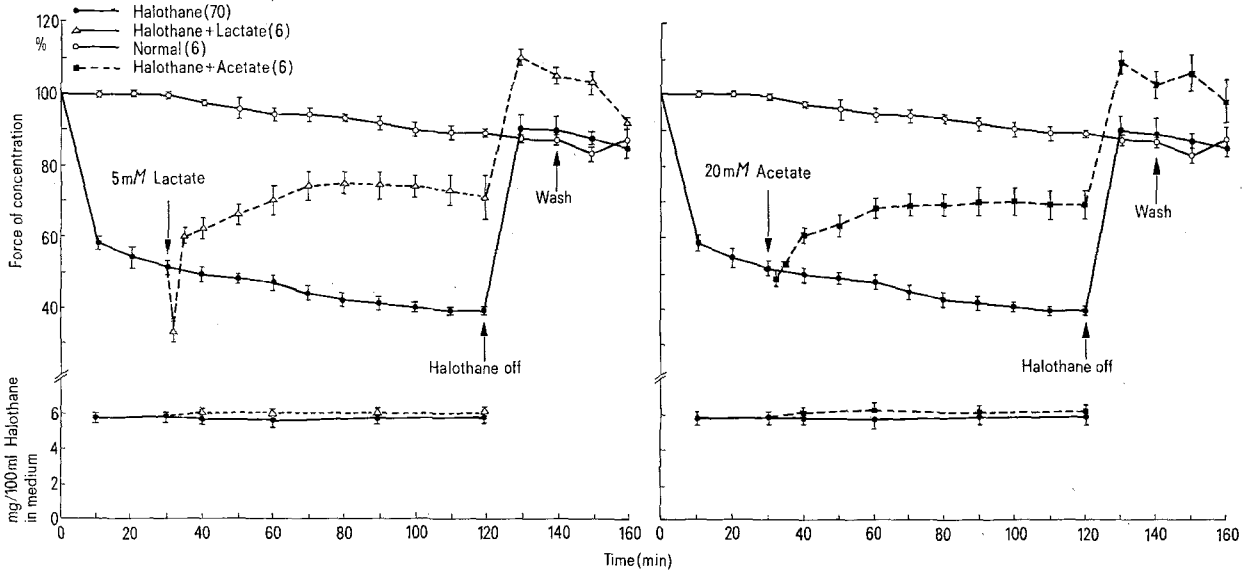

Fig. 1. Effect of lactate (5 m*M*) or acetate (2.5 m*M*) on atria depressed with halothane. In this and subsequent figures, halothane was added at zero time (i.e. following a 60 min equilibration period in the normal Krebs-Ringer bicarbonate glucose medium). Substrates were added 30 min after start of halothane administration. Vertical bars represent 1 SE of the mean.

Results. Effects of lactate or acetate on atria depressed with halothane. Sodium lactate (5 m*M*) or sodium acetate (2.5 m*M*) was added to the bathing medium 30 min after the start of the halothane administration. The Figure 1 shows that, despite the continued administration of halothane and maintenance of the halothane concentration (approximately 6 mg/100 ml mean value) in the medium, the addition of either lactate or acetate produces a gradual and partial increase in the force of contraction of atria depressed with halothane similar to that previously demonstrated with pyruvate. The maximally effective concentration of lactate was 5 m*M* and of acetate 2.5 m*M*.

Effect of additional glucose on atria depressed with halothane. Since the early report by LOCKE and ROSENHEIM[4], the glucose metabolism in the heart has been well studied. MASUOKA et al.[5] have reported that glucose was ineffective in increasing the amplitude of contraction of ventricle strip depressed by iodoacetate, but pyruvate caused a marked stimulation. Similar investigations with 2-desoxyglucose on isolated rat atria have recently been reported by GIMENO et al.[6]. If it is assumed that the cardiac depressant action of halothane may be similar to the action of these enzyme inhibitors on glucose metabolism of the heart, the experiments to test the effects of glucose at different concentrations on the halothane-depressed atria may have bearing on the problem of the action of halothane on the myocardium. The results presented in Figure 2 show that the addition of glucose at either 5 or 20 m*M* concentration produces little change in the contractile force of halothane-depressed atria. The data obtained from these series of experiments are consistent with the previous report with iodoacetate[5] or 2-desoxy-glucose[6] and indicate that there is some defect in glucose utilization of the heart induced by halothane.

Relative abilities of substrates to restore the contractile activity of atria depressed with halothane. It is evident from Figure 3 that recovery of the force of contraction from the depression by halothane occurred to varying degrees with pyruvate, lactate and acetate. The greatest effect was produced by lactate, while pyruvate, and acetate were less effective. High concentrations of glucose were not effective at any concentration tested. The resutls obtained with pyruvate, lactate and acetate are similar to previous reports[5,7] in which the force of contraction of substrate-depleted rat heart was stimulated by addition of these substrates.

Discussion. It has been well demonstrated that glucose, pyruvate, and acetate can be metabolized for the purpose of sustaining the contractile process of the myocardium[5–12]. Results obtained from the cardiac preparations in vitro suggest that either the uptake of glucose or operation of the glycolysis are important for a fraction of the myocardial contractility, inasmuch as pyruvate is only partially effective in restoring the developed tension in the absence of glucose or during block of glycolysis with enzyme inhibitors[5,6,13], or with bicarbonate-free medium[14].

In Figure 1 we have found that lactate and acetate partially restored the reduced contractility of halothane-treated atria, similar to that previously demonstrated with

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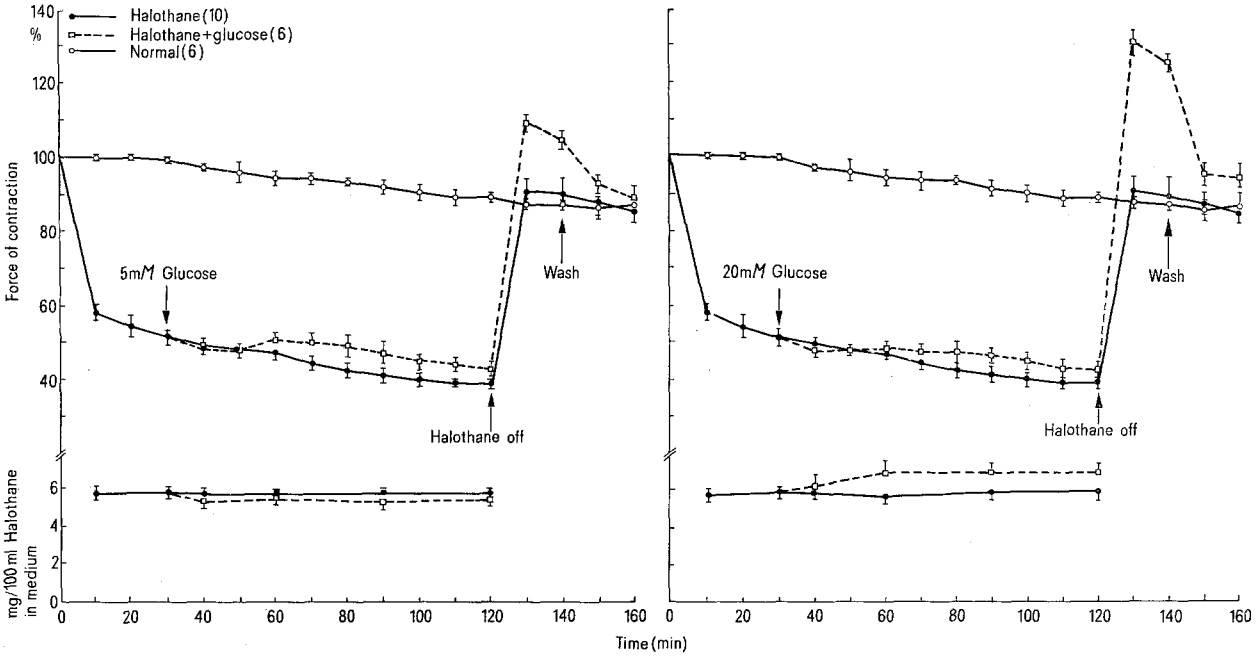

Fig. 2. Effect of additional glucose (5 m*M* and 20 m*M*) on halothanedepressed rat atria.

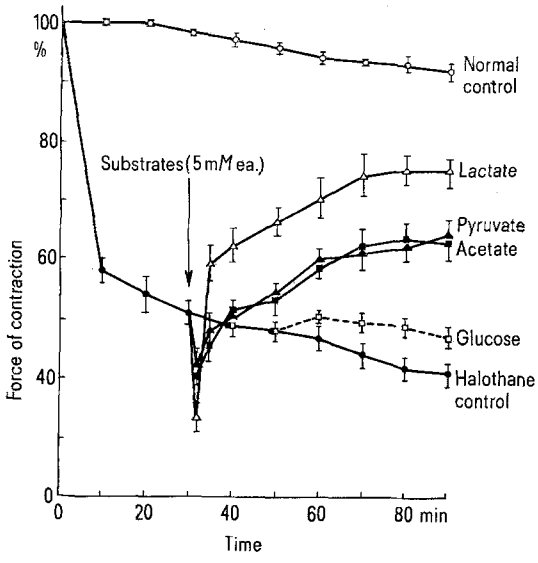

Fig. 3. Comparative effects of substrates (5 mM) on halothane-depressed rat atria.

pyruvate. The results obtained with these experiments are consistent with the considerable data in the literature that lactate, acetate and pyruvate were effective in increasing the substrate-depleted rat ventricle strips[5] and those in bicarbonate-free medium[15] in which glucose metabolism on the heart was impaired[16]. In Figure 2, it was shown that glucose at any concentration tested was ineffective in increasing the declined contractility of rat atria by halothane. The data obtained from these experiments are similar to those in the previous reports that glucose was ineffective in restoring the force of contraction of rat atria depressed by 2-desoxyglucose[6] or by bicarbonate-free medium[14]. Glucose was also ineffective in restoring the amplitude of contractility of rat ventricle strips depressed by iodoacetate[5].

Thus, our results are consistent with the hypothesis that halothane exerts at least a part of its negative inotropic effect on rat atria by inhibiting either the uptake or utilization of glucose via the glycolytic pathway. The site of blockade must be prior to the conversion of pyruvate to acetyl CoA.

Zusammenfassung. Nachweis, dass die nach Halothan eingetretene Verminderung der Kontraktilität des Myokards durch Lactat oder Acetat verhindert werden kann. Das Ergebnis stützt die Hypothese, Halothan hemme die Aufnahme von Glykose oder beeinträchtige deren Verwertung.

KYE-CHANG KO[17] and R. PARADISE

Department of Pharmacology School of Medicine, Kyung Hee University, Dongdaemoon-ku, Seoul (Korea); and Department of Pharmacology, Indiana University, Bloomington (Indiana, USA), 26 August 1974.

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Brain Abnormalities in the Lurcher (*Lc*) Mutant Mouse

Lurcher (symbol *Lc*) is a mouse mutant first discovered and described by PHILLIPS[1]. The mutation arose spontaneously in a White (Mi^{wh}) homozygote and is expressed as a semidominant in heterozygotes (*Lc*/+). The *Lc* gene is on chromosome 6 (linkage group XI). Homozygotes (*Lc*/*Lc*) are believed to die during the early neonatal period. Heterozygotes are fertile, although the litter size of *Lc*/+ females is reduced. Lurcher body weights of both sexes are less than those of normal counterparts.

Lurcher heterozygotes show abnormal behavioral characteristics consisting of ataxia with a tendency to fall to either side[1,2]. These animals also tend to walk backward when placed outside of the cage on a smooth surface[1]. Although lurcher has been classified as a neuromuscular mutant, little is known about the morphology of the nervous system in these animals. However, lurcher manifests many of the behavioral characteristics which have been described in the mutant reeler (*rl*) in which the cerebellum has been shown to be defective[3–6]. Since several other cerebellar mutants such as staggerer (*sg*), weaver (*wv*), and nervous (*nr*) also exhibit ataxic behavior[2,6–11], the present study was undertaken to obtain information on the gross structure of the brain, particularly the cerebellum, in the lurcher mutant mouse.

Materials and methods. The lurcher mutant colony used in this study was originally derived from a male lurcher heterozygote (*Lc*/+) carrying the translocation T(2:6) 7Ca who was mated to C57BL/6J females. *Lc*/+ progeny were subsequently backcrossed to C57BL/6J individuals for several generations. Lurcher (*Lc*/+) and normal (+/+) littermates of both sexes were sacrificed at ages ranging from birth to approximately 10 months of age. The brains were quickly removed and wet weights were determined. The brains were then fixed for 4 to 5 days in Bouin's solution, transferred to 70% ethanol, and examined at magnifications up to 60×. The nomenclature of SIDMAN et al.[12] was used to describe gross features of the mouse brain.

Results. Lurcher (*Lc*/+) mice in our colony show a hesitant, lurching gait as well as a tendency toward tonic-clonic seizures, particularly when suddenly disturbed. This behavior is clearly manifested on approximately the 12th day after birth. Prior to this time the pale coat, light

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