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麻醉劑의 心臟藥理學的 硏究

第 2 報 各種代謝基質에 對한 Halothane 低下遊離心房의 收縮反應

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Cardiac Pharmacology of Anesthetics

2. Contractile Response of Halothane-Depressed Isolated Atria to Various Metabolizable Substrates

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ABSTRACT

Further elucidation of the mechanism of halothane's negative inotropic action has resulted from a study of the effect of various substrates on halothane-depressed rat atria. Approximately 6 mg% halothane was required to maintain a 50 % depression of the contractility of rat atria suspended in a modified Krebs-Ringer bicarbonate glucose medium, pH 7.4, 30°C for 2hr. Both lactate and acetate were found to restore partially the contractility of halothane-depressed atria. The maximally effective concentration of lactate was 5 mM; for acetate it was 2.5 mM. Neither 5 nor 20 mM of additional glucose was effective in restoring the force of contraction of halothane-depressed atria. The 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 by the myocardium. The site of blockade must be prior to the conversion of pyruvate to acetyl CoA.

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 Krebs-Ringer bicarbonate glucose medium; 2) pyruvate partially restores the contractility of halothane-depressed atria, but has no effect on normal atria; the partial recovery of depressed atria by the addition of sodium pyruvate is due to the effect of the pyruvate ion itself, not to the sodium ion; 4) addition of pyruvate, to atria depressed with hypertonic medium, produced only further depression. 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.

METHODS

Atria from decapitated rats were suspended in a modified Krebs-Ringer bicarbonate glucose medium aerated with 95% O_2~5% CO_2 at 30°C and pH 7.4, and electrically stimulated at a rate of 200/min as previously described[2]. Halothane was administered into the medium by means of the anesthetistat[3]. The halothane concentration in the medium was determined at 10 to 30 min intervals with a gas chromatograph throughout the experimental period[3].

RESULTS

Effects of lactate or acetate on atria depressed with halothane.

Experiments were performed to determine whether lactate or acetate had a similar action to pyruvate on the halothane-depressed atria.

Approximately 50% depression of the force of contraction of isolated rat atria was attained with halothane according to the experimental procedure previously described[1]. Halothane administration was begun at zero time (following a 1hr equilibration period). Adjustments in the anesthetistat used to deliver the halothane were made as necessary during the first 30 min in order to achieve 50% depression of the contractility. Following this 30 min period no further adjustments were made. Relatively stable concentrations of halothane were observed in the bathing medium during the experimental period (approximately 6 mg% mean value).

Sodium lactate(5 mM) or sodium acetate(2.5 mM) was added to the bathing medium 30 min after the start of the halothane administration. The fig. 1 shows that despite the continued administration of halothane and maintenance of the halothane concentration in the medium, the

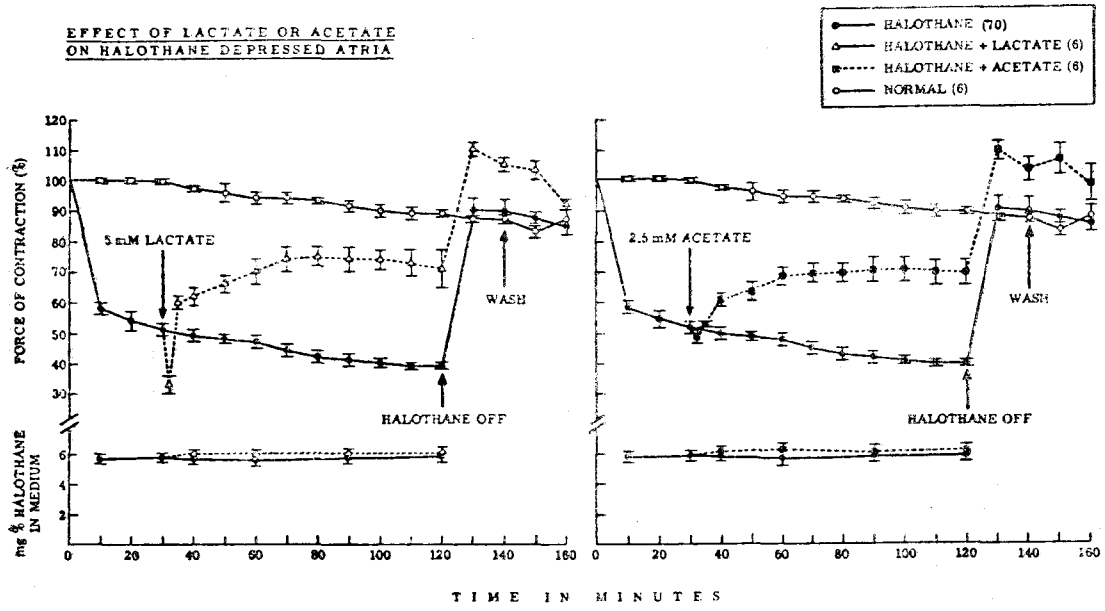

Fig. 1. Effect of lactate(5 mM) or acetate(2.5 mM) on atria depressed with halothane. In this and subsequent figures halothane was added at zero time(i.e. following a 60 min equilibration period in the normal Krebs-Ringer bicarbonate glucose medium). Substrates were added 30 min after start of halothane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

addition of either lactate or acetate produced a gradual and partial increase in the force of contraction of atria depressed with halothane similar to that previously demonstrated with pyruvate. A similar recovery in the force of contraction was also observed in both cases of lactate after stopping the halothane administration. The maximally effective concentration of lactate was 5 mM and of acetate 2. 5 mM.

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 contration of ventricle strip depressed by iodoacetate, but pyruvate caused a marked stimulation. Similar investigations with 2-desoxy-glucose 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 effect 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 fig. 2 show that the addition of glucose at either 5 or 20 mM concentration rpoduced little change in the force of contraction of atria depressed with halothane. The data obtained from these series of experiments are consistent with the previous demonstrations with iodoacetate[5] or 2-desoxy-glucose[6] and indicate that there is some defect in glucose utilization of the heart induced by halothane.

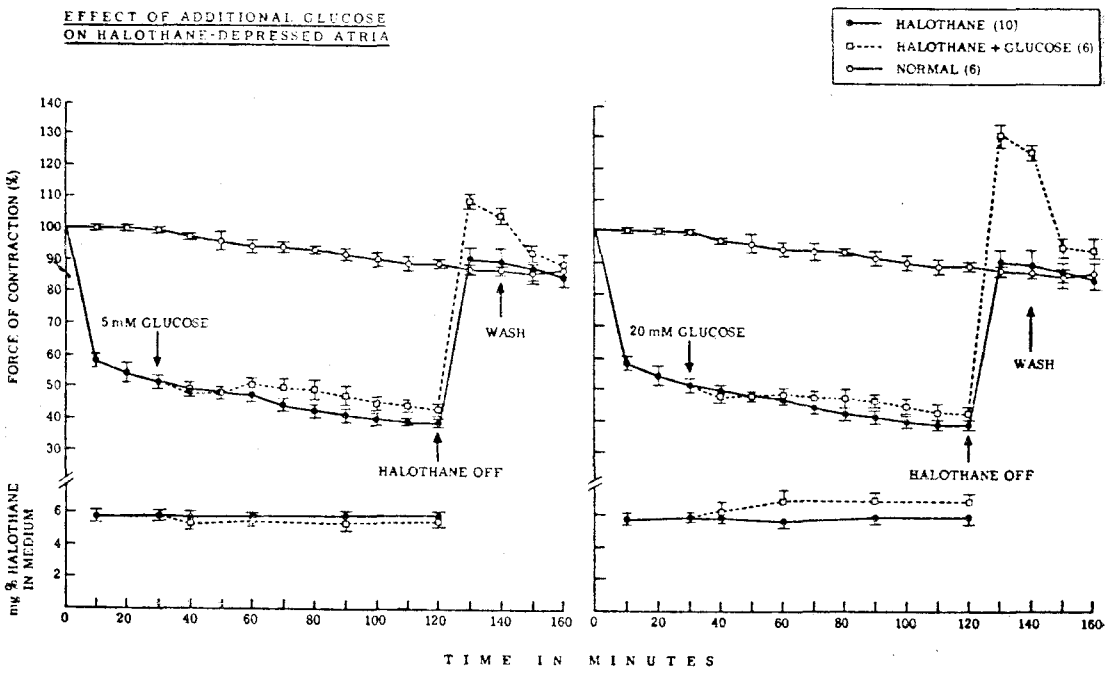

Fig. 2. Effect of additional glucose(5 mM and 20 mM) on the force of contraction of rat atria depressed with halothane.

Relative abilities of substrates to restore the contractile activity of atria depressed with halothane.

Effect of substrates at a concentration of 5 mM on the contractility for at atria depressed with halothane are seen in fig. 3. It is evident 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 than lactate. High concentrations of glucose were not effective at any concentration tested. The results 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

We have previously reported that pyruvate

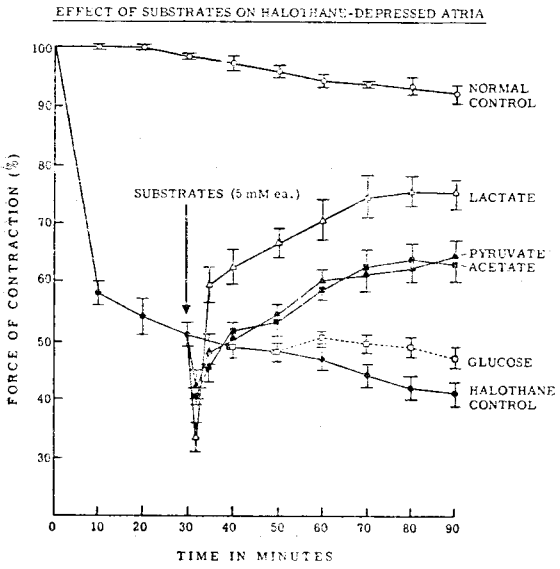

Fig. 3. Comparative effects of substrates(5 mM) on the force of contraction of rat atria depressed with halothane.

partially restored the force of contraction of rat atria depressed with halothane despite the continuation of halothane administration, and have considered the possibility that the myocardial depression induced by halothane is caused by inhibition of the mechanism for uptake or utilization of glucose in the heart[1]. The findings in the present study that lactate and acetate were effective in increasing the contractile activity of isolated rat atria depressed with halothane are consistent with the data previously demontsrated with pyruvate.

The utilization of substrates has been well studied in cardiac preparations, and it has been 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 suggest that either the uptake of glucose or the operation of the glycolytic pathway are important for a fraction of the contractile activity of the myocardiun, in as much 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 diaphragm muscle the Embden-Meyerhof pathway was inhibited at the phosphofructokinase step when the tissue was incubated in bicarbonate-free medium[15]. Current interpretations emphasize the phosphofructokinase reaction as an important regulatory step of the glycolysis in the cells[16~18].

In fig. 1 we have found that lactate and acetate and acetate partially restored the reduced contractility of halothane-treated atria similar to that previously demons trated with 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[19]

in which glucose metabolism of the heart was impaired[20] and/or the glycolytic pathway was inhibited[15].

In fig. 2, it was shown 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 ampilitude of contractility of rat ventricle strips depressed by iodoacetate[5].

We have also demonstrated in the previous publication[1] that 5 mM sodium chloride was ineffective in restoring the force of contraction of halothane-depressed atria when atria when administered under the same conditions where sodium pyruvate was effective. This indicates that the effect of sodium lactate are due to lactate or acetate itself similar to that with pyruvate.

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.

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