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Contractile Response of Lidocaine-Depressed Isolated Atria in the Absence of Glucose

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ABSTRACT

The contractility of isolated rat atria, suspended in Krebs-Ringer bicarbonate medium containing 5.5mM glucose, was depressed approximately 50% by 0.1mM of lidocaine. Partial recovery of the lidocaine-depressed contractility was achieved by the metabolizable substrates pyruvate, acetate, and fructose, but not by addition of glucose. Glucose produced the dose-dependent increase in the force of contraction of normal atria, whereas pyruvate, acetate, and fructose produced no significant effect in the contractile activity of the normal atria. In the absence of exogenous glucose lidocaine produced more marked depression of atrial contractility than that in the presence of exogenous glucose.

The results of this study may confirm that the utilization of cardiac glycogen is also inhibited by lidocaine at sites of the glucose phosphate isomerase step or step between glycogen to glucose-6-phosphate.

Key Words: Lidocaine, Heart, Substrates, Contractility, Glycogen

INTRODUCTION

This investigation is a continuation of a series from our previous reports dealing with the mechanism of the cardiac depressant action of inhalation anesthetics (Ko and Paradise, 1969a, 1970b, 1971b, 1971c, 1972a, 1972b, 1973a, 1975) and barbiturates (Ko and Yoon, 1980; Ko, 1981; Ko and Paradise, 1983; Ko, 1989) on isolated rat atria and human hearts. Having ruled out interference with the supply of oxygen by halothane as the basis for its depressant action (Paradise and Griffith, 1966), we next focused our attention on glycolysis. That pyruvate in rat and human atria, and acetate, lactate, and fructose in rat atria, could overcome the contractile depression induced by halothane, while glucose was ineffective in rat and human atria, suggested that halothane was blocking an early step in glycolysis (Ko and Paradise, 1969a; Paradise and Ko, 1970; Ko and Paradise, 1970a, 1970b). Since fructose apparently is metabolized via the phosphofructokinase step (Paradise and Ko, 1970; Ko and Paradise, 1970c), the probable sites of halothane blockade were confirmed to: 1) uptake of glucose into the cell; 2) phosphorylation of glucose to glucose-6-phosphate by hexokinase; or 3) conversion of glucose-6-phosphate to fructose-6-phosphate by glucose phosphate isomerase (Paradise and Ko, 1970).

It is evident that local anesthetic lidocaine also depress the cardiac function (Austen and Moran, 1965; Contantino *et al.*, 1969; De Jong *et al.*, 1973; Kahn *et al.*, 1982; Liu *et al.*, 1982; Sage *et al.*, 1983; Lim and Kim, *et al.*; Ko *et al.*, 1986).

It has been demonstrated that the cardiac depressant action of lidocaine is at least partly linked to a block at an early step or steps in the glycolytic pathway in the heart, as shown by the abilities of pyruvate, acetate, and fructose, but not glucose, to

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produce a positive inotropic effect in rat atria depressed by lidocaine (Lim and Kim, 1984; Ko and Sohn, 1986), similar to those from the experiments with inhalation anesthetics (Ko and Paradise, 1969a; Paradise and Ko, 1970) and barbiturates (Ko, 1989). In this investigation we have attempted to localize further the site of lidocaine action by the use of glucose-free medium.

MATERIALS AND METHODS

Male rats weighing 180 to 200g were decapitated, and the atria were removed and suspended in modified Krebs-Ringer bicarbonate glucose medium (Gimeno *et al.*, 1965, 1966, 1969).

The medium was gassed with 95% O_2-5% CO_2 at pH 7.4 and 30°C. The mechanical activity of rat atria electrically stimulated at a rate of 200 per minute in the medium was determined using a sensitive strain gage as previously described (Gimeno *et al.*, 1966; Ko *et al.*, 1969b; Ko and Paradise, 1973a).

In the experiments with substrate-free medium, the normal Krebs-Ringer bicarbonate glucose medium was changed to substrate-free medium (free of glucose) following the one-hour equilibration period.

RESULTS

Effects of substrates on lidocaine-depressed atria

Various substrates were added to the bathing medium 30 minutes after the atria were depressed approximately 50% with 0.1mM lidocaine. It is evident from Fig. 1 that pyruvate, acetate, and fructose partially restored the force of contraction of isolated rat atria depressed with lidocaine, but additional glucose was without effect. The results are in agreement with the previous reports (Lim and Kim, 1984; Ko and Sohn, 1986).

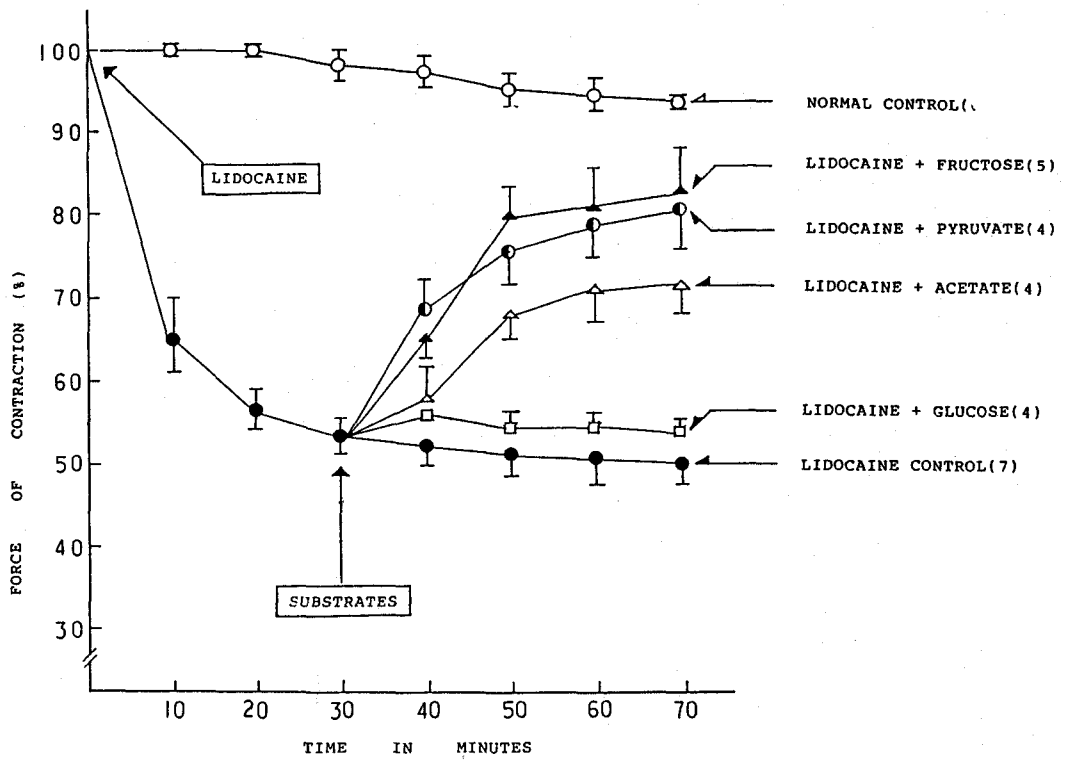

Fig. 1. Effects of substrates on contractility of isolated rat atria depressed with lidocaine (0.1mM). Substrates were added 30 minutes after the addition of lidocaine (0.1mM). In this and subsequent figures, lidocaine was added at zero time (following a 60 minutes equilibration period in the normal Krebs-Ringer bicarbonate glucose medium). Vertical bars represent ± one standard error of the mean. Parentheses represent number of experiments.

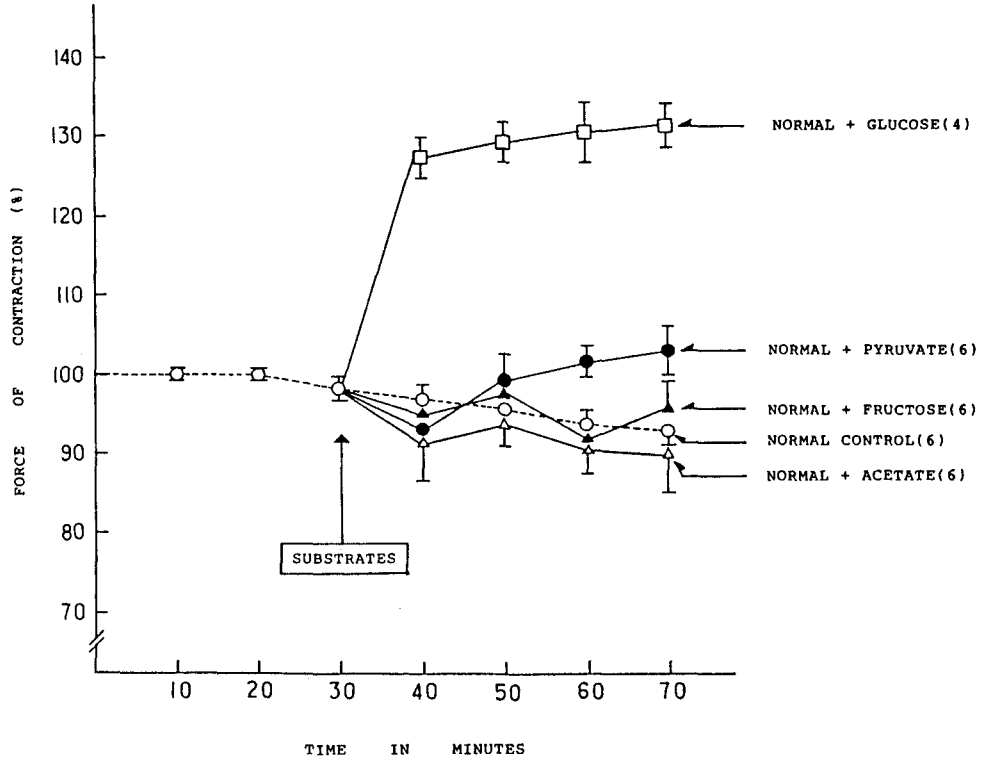

Fig. 2. Effects of substrates on contractility of isolated rat atria in the normal Krebs-Ringer bicarbonate glucose medium. 20mM glucose, 5mM pyruvate, 30mM fructose, and 5mM acetate were added 30 minutes after the equilibration in the normal medium. Vertical bars represnet ± one standard error of the mean. Parentheses represent number of experiments.

Effects of substrates on normal atria

Atria were equilibrated for 60 minutes in the Krebs-Ringer bicarbonate glucose medium prior to the experiments. Thirty minutes after the equilibration period, sodium pyruvate (5mM), sodium acetate (5mM), fructose (30mM), and glucose (20mM) were administered to the normal atria. It is evident from Fig. 2 that pyruvate and acetate, in concentrations effective in the lidocaine-depressed atria, had no positive inotropic effect. The Fig. 2 also shows that glucose, in concentration ineffective on the lidocaine-depressed atria, produced marked dose-dependent increases in contractility of normal atria.

Effect of lidocaine on atrial contractility in substrate-free medium

In order to compare the effects of lidocaine in the absence of glucose with its effect in the presence of glucose, it was necessary to insure that equal concentrations of lidocaine were administered in both circumstances.

After a one-hour equilibration period, the normal Krebs-Ringer bicarbonate glucose (5.5mM) medium was replaced with substrate-free medium (omission of glucose from the normal medium). The results are summarized in Fig. 3. After 15 minutes incubation of atria in this substrate-free medium, 0.1mM of lidocaine was added to atria whose contractility was depressed about 20% at the time. It is evident from the Fig. 3 that the force of contraction of atria declined due to prolonged activity in substrate-free medium, in comparison with the normal control level (Fig. 1). However it is also evident from the Fig. 3 that the contractile activity of substrate-free treated atria were markedly depressed (more than about 70% depression) by lidocaine, in comparison to the substrate-free control levels (about 50% depression). It was also observed from the Fig. 3 that the replacement of the substrate-free

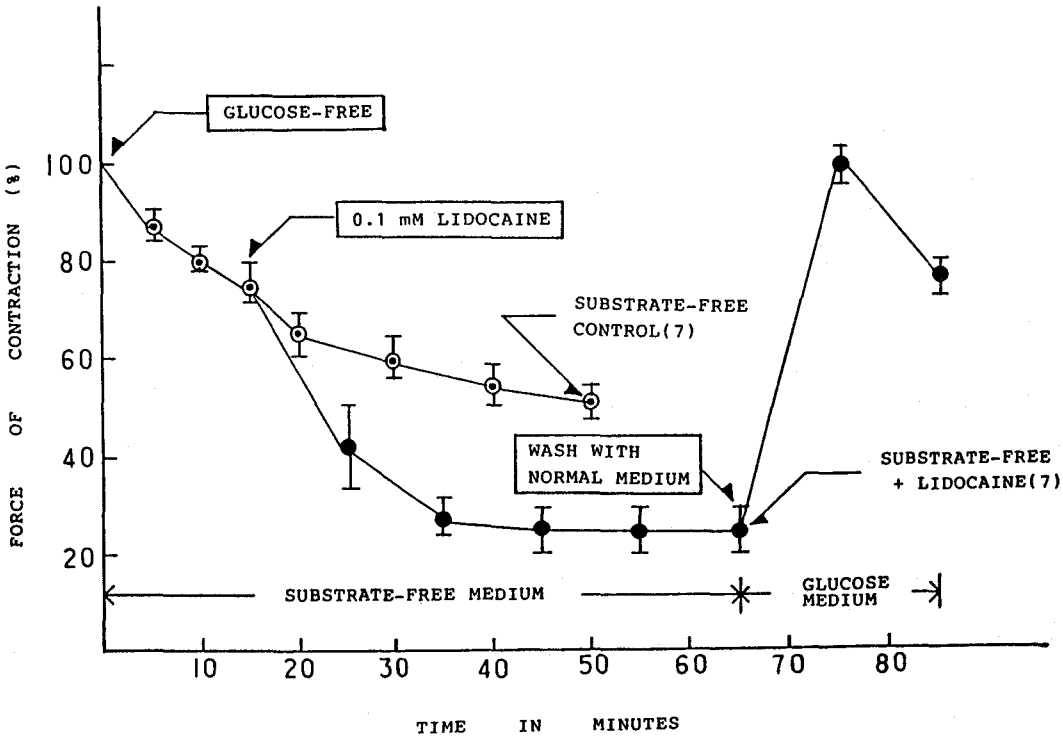

Fig. 3. Effects of lidocaine on contractility of isolated rat atria in the absence of glucose. Zero time represents one hour in the normal medium. At zero time the normal medium was changed to substrate-free medium (free of glucose). 15 minutes later 0.1mM of lidocaine was administered to this substrate-free medium. Vertical bars represent ± one standard error of the mean. Parentheses represent number of experiments.

medium with normal glucose medium completely restored contractility of the lidocaine-depressed rat atria to the control levels.

DISCUSSION

This investigation is a continuation of studies dealing with the mechanism of the cardiac depressant action of lidocaine. In the previous investigation, it was found that metabolic substrates pyruvate, acetate, and fructose were partially effective in restoring the contractile activity of isolated rat atria in the hypodynamic state induced by lidocaine, whereas additional glucose at any concentration tested had no significant effect on the contractility of lidocaine-depressed atria (Fig. 1). However, it has been demonstrated in the literature (Ko and Paradise, 1973b) that additional glucose produced the dose-dependent increase in the force of contraction of normal atria, whereas the addition of pyruvate, acetate, and fructose produced no significant effect in the contractile activity of the normal atria (Fig. 2). From the results with above experiments, it is concluded that at least part of negative inotropic action of lidocaine is the result of inhibition of glucose uptake or inhibition of glucose utilization in the glycolytic pathway of the heart (Lim and Kim, 1984; Ko and Sohn, 1986). That fructose was also effective in the lidocaine-depressed atria and appeared to be metabolized via phosphofructokinase (PFK) step indicated that the sites of blockade is above the PFK and localized to sites of glucose uptake, hexokinase step, or the glucose phosphate isomerase step.

In this study it was demonstrated that in the absence of exogenous glucose lidocaine produced more marked depression of atrial contractility than that in the presence of exogenous glucose (Fig. 3). In the glucose-free experiments there is no exogenous glucose to be taken up or to be metabolized, so atria exposed to this substrate-free medium must rely on endogenous substrate stores, probably cardiac

glycogen, to provide energy for contraction (Ko, 1977).

The results of these experiments with substrate-free medium extremely indicate that a block at sites of the glucose phosphate isomerase (glucose-6-phosphate to fructose-6-phosphate) step or step between glycogen to glucose-6-phosphate would reduce the utilization of cardiac glycogen and lead to reduction in the atrial contractility by lidocaine, as observed in the Fig. 3.

That glycogen is an important fuel for the contractile process of the myocardium is evidenced by the finding that bicarbonate-free medium and citrate, both inhibitors of PFK (Paradise and Ko, 1970; Ko and Paradise, 1970c), cause more rapid decreases in the atrial contractility than glucose-free medium. If fatty acid or some substrate below the PFK step were very important for the maintenance of contractility in the absence of glucose, bicarbonate-free medium and citrate would not have blocked these pathways and the rates of depression induced by these inhibitors would have been similar to that induced by glucose-free medium. Thus, it appears that glycogen utilization is an important factor in maintaining contractility in the absence of glucose and that lidocaine interferes with this utilization of the cardiac glycogen.

This investigation does not rule out the possibility of multiple sites of blockade. In conclusion, our results indicate that if only a single site of glycolysis is blocked by lidocaine in the substrate-free medium, the utilization of cardiac glycogen is also inhibited by the lidocaine at site to be the conversion of glucose-6-phosphate to fructose-6-phosphate isomerase.

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= 국문초록 =

Lidocaine에 의해 억제된 적출심방의 수축력에 대한 Glucose제거의 영향

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Lidocaine의 심근 수축력 억제작용의 기전을 규명하기 위한 일환으로 정상 Krebs-Ringer bicarbonate glucose 용액에서 각종 대사기질이 lidocaine 억제심방과 정상심방의 수축력에 미치는 영향, 그리고 glucose 제거용액에서 lidocaine의 심방 수축력에 대한 영향을 검토하여 다음과 같은 결과를 얻었다.

1. Pyruvate(5mM), acetate(5mM), fructose(30mM)는 lidocaine에 의해 감소된 심방 수축력을 현저히 증가시켰으나, 정상심장에는 별 영향이 없었다.
2. Glucose(20mM)는 lidocaine 억제심방의 수축력을 증가시키지 못하였으나 정상심방의 수축력을 현저히 증가시켰다.
3. Glucose 제거용액에서 lidocaine은 정상용액에서보다 심방 수축력을 현저히 더 감소시켰다.

이상의 결과로 보아 lidocaine은 적출심장에서 외인성 glucose를 제거시, 심장 glycogen의 이용을 glucose phosphate isomerase 단계 혹은 glycogen이 glucose-6-phosphate로 전환되는 단계를 억제한다는 것을 시사하고 있다.