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The Effects of Metabolic Substrates on Contractility of Isolated Rat Atria Depressed with Bupivacaine

Seung-Joon Park, Joo-Ho Chung, Jee-Chang Jung and Kye-Chang Ko

Department of Pharmacology, College of Medicine, Kyung Hee University, Seoul 130-701, Korea

ABSTRACT

A concentration of 0.01 mM bupivacaine was necessary to maintain approximately 50% depression of contractility of rat atria suspended in a modified Krebs-Ringer bicarbonate glucose medium, pH 7.4 at 30°C. Sodium pyruvate, sodium acetate, and fructose partially restored the contractility of the bupivacaine-depressed atria. However, 20 mM glucose had no effect on the bupivacaine-depressed atria, although this concentration of glucose markedly increased the contractility of normal atria not to be exposed to bupivacaine. Contractility of normal atria was not significantly influenced by sodium pyruvate, sodium acetate, and fructose.

The results suggested that at least part of the negative inotropic action of bupivacaine is the result of inhibition of glucose uptake or utilization in the glycolytic pathway, and further pinpoint the blockade as an early step in the glycolytic sequence prior to the phosphofructokinase step.

Key Words: Bupivacaine, Heart, Substrates, Contractility, Glycolysis

INTRODUCTION

Since the cardiac depressant action of anesthetic agents have attracted attention, the negative inotropic effects of inhalation anesthetics and barbiturates are well documented (Brown and Crout, 1971; Goldberg and Ullrick, 1967; Komai and Rusy, 1983; Paradise and Bibbins, 1969; Paradise and Griffith, 1965, 1966; Rusy and Komai, 1987; Shibata *et al.*, 1989; Shimosato *et al.*, 1969).

This report is a continuation of a series from our laboratory dealing with the mechanism of cardiac depressant action of anesthetics by initially utilizing isolated rat atria (Ko and Paradise, 1969, 1971a, 1971b, 1971d, 1972, 1973b, 1975; Ko *et al.*, 1972; Paradise and Ko, 1970), and subsequently using isolated human atria obtained during cardiac surgery (Ko and Paradise, 1970a). Ko and Paradise have investigated the effects of inhalation anesthetics on carbohydrate metabolism of isolated rat heart and isolated human heart by the use of various exogenous substrates as metabolic tools, and it has been postulated that the cardiac depressant action of inhalation anesthetics 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 produce a positive inotropic effect in rat atria depressed by the general anesthetics (Ko and Paradise, 1969, 1971a, 1971d, 1972, 1973b; Krishina and Paradise, 1972). Biochemical supports for this theory were demonstrated in isolated rat atria (Morrow and Paradise, 1972, 1974). Functional studies further pointed to the glucose phophate isomerase step as the step inhibited by these anesthetics (Ko and Paradise, 1971a, 1971b). Ko and co-workers have investigated the effects of intravenous anesthetics pentobarbital and thiopental on carbohydrate metabolisms in isolated rat heart, and the results were similar to those of inhalation anesthetics (Ko, 1981; Ko *et al.*, 1986; Lim and Kim, 1984). And it has been previously

reported that pyruvate and acetate partially restored the contractility of isolated rat atria depressed approximately 50% with lidocaine (0.1 mM) or procaine (0.3 mM), despite the fact that additional glucose had no significant effect on the depressed contractility (Ko, 1987; Lim and Kim, 1984). These findings suggested that at least part of the negative inotropic effects of lidocaine or procaine are the results of inhibition of glucose uptake, or inhibition of glucose utilization in the glycolytic pathway of the heart. The site of blockade by these local anesthetics must precede the conversion of pyruvate to acetyl CoA. Recently, it is demonstrated that another metabolic substrate fructose also produced marked increase in the force of contraction of isolated rat atria depressed with lidocaine or procaine, and further suggested that the blockade by these local anesthetics may be at early step in the glycolytic sequences prior to the phosphofructokinase (PFK) step in the heart (Ko, 1987; Ko *et al.*, 1986).

Bupivacaine can cause a variety of cardiac toxicities (Baselt and Cravery, 1989; Clark *et al.*, 1988; Covino, 1987; Ritchie and Greene, 1990; Thomas *et al.*, 1986). However, the mechansim on the myocardial effects of bupivacaine has not been clearly documented in relation to the cardiac metabolism.

The purpose of this study is to present a basic data on the functional response of isolated rat atria to local anesthetic agent bupivacaine, and to determine the effects of metabolic substrates on the contractile activity of bupivacaine-depressed isolated atria, in order to ascertain whether the cardiac depressant action of bupivacaine is related to the substrate utilization of the myocardium, similar to that of inhalation anesthetics halothane and methoxyflurane.

MATERIALS AND METHODS

Male rats weighing 150 to 200 g were decapitated, and the atria were removed and suspended in modified Krebs-Ringer bicarbonate glucose medium (Gimeno *et al.*, 1965).

The medium was gassed with 95% O_2 and 5% CO_2 at pH 7.4 and 30°C. A constant tension of 750 mg was maintained throughout the experiments. 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 (Ko and Paradise, 1973b).

In the experiment with local anesthetic bupivacaine, the administration of bupivacaine was begun at zero time following a one-hour equilibration period. In the experiments with metabolic substrates, sodium pyruvate, sodium acetate, fructose, and glucose were used. In the experiments with hypertonic medium, the increment of osmotic pressure was made by the addition of NaCl at a concentration of 100 mM to the normal Krebs-Ringer bicarbonate glucose medium. For the experiments, the normal Krebs-Ringer bicarbonate glucose medium was changed to this hypertonic medium following the one-hour equilibration period.

RESULTS

Effects of bupivacaine on atrial contractility

The behaviour of atria in the presence of bupivacaine was determined to provide basic data with which response to metabolic substrates on the depressed atria could be compared. Hence, dose-response curve of bupivacaine on the normal atrial contractility were first determined, if or what concentrations of bupivacaine decline 50% depression of the force of contraction of atria.

After a one-hour equilibration period, bupivacaine was added to the bathing medium in which the normal atria were beating. The employed bupivacaine was made at a concentration of 0.005, 0.01, and 0.02 mM. The results obtained from these series of experiments are shown in Fig. 1. It is evident from the Fig. 1 that the bupivacaine at a concentration of 0.01 mM produced approximately 50% depression in the force of contraction of atria at 30 minutes after the administration of bupivacaine, and the declined degree of atrial contractility was almost kept constant levels during a 60 minutes of experimental period.

It is also evident from the Fig. 1 that bupivacaine at a concentration of 0.005 mM produced only approximately 30% depression of the contractility, but 0.02 mM of bupivacaine produced approximately 70% decrement of the contractile force of atria.

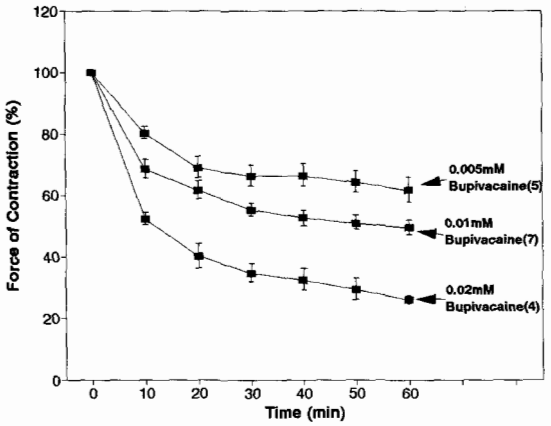

Fig. 1. Dose-response curve of bupivacaine on contractility of isolated rat atria. Bupivacaine at concentration of 0.005, 0.01, and 0.02 mM was added at zero time(following 60 minutes equilibration period in the Krebs-Ringer bicarbonate glucose medium). Each value represented as mean±standard error. Parentheses represent number of experiments. Temperature 30°C, pH 7.4.

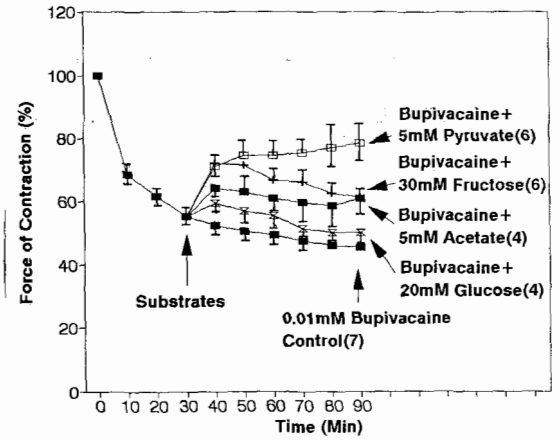

Fig. 2. Effects of substrates on bupivacaine-depressed rat atria. After a one hour equilibration period in normal Krebs-Ringer bicarbonate glucose medium, 0.01 mM of bupivacaine was administered. 5 mM pyruvate, 5 mM acetate, 30 mM fructose, and 20 mM glucose were added at 30 minutes after administration of 0.01 mM bupivacaine. Each value represented as mean± standard error. Parentheses represent number of experiments. Temperature 30°C, pH 7.4.

Effects of substrates on atria depressed with bupivacaine

After a 60 minutes equilibration period in the normal Krebs-Ringer bicarbonate glucose medium, addition of bupivacaine at concentration of 0.01 mM produced approximately 50% depression of the force of contraction of isolated rat atria (Fig. 1). Thus, this concentration of bupivacaine was chosen for the substrate study because it produced about the same degree of depression of the contractile activity as that seen with inhalation anesthetics (Ko and Paradise, 1969, 1971b, 1972, 1973b) and other cardiac depressants (Ko and Paradise, 1971c; Ko *et al.*, 1969).

Substrates (5 mM sodium pyruvate, 5 mM sodium acetate, 20 mM glucose, and 30 mM fructose) were added to the bathing medium 30 minutes after the atria were depressed approximately 50% with 0.01 mM of bupivacaine. It is evident from Fig. 2 that pyruvate, acetate, and fructose partially restored the contractility of atria depressed by bupivacaine, but glucose was without effect.

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 (5 mM), sodium acetate (5 mM), fructose (30 mM), and glucose (20 mM) were added to the bathing medium in which normal atria were beating. It is evident from Fig. 3 that pyruvate, acetate, and fructose, in concentrations effective on the bupivacaine-depressed atria, had no positive inotropic effect. The Fig. 3 also shows that glucose, in concentration ineffective on the bupivacaine-depressed atria, produced marked increase in force of contraction of normal atria.

Effects of substrates on atria depresssed in hypertonic medium

Experiments to further clarify the positive inotropic effects of substrates on the bupivacaine-depressed atria were designed by introducing the different experimental conditions. Hypertonic medium, prepared by the addition of 100 mM sodium

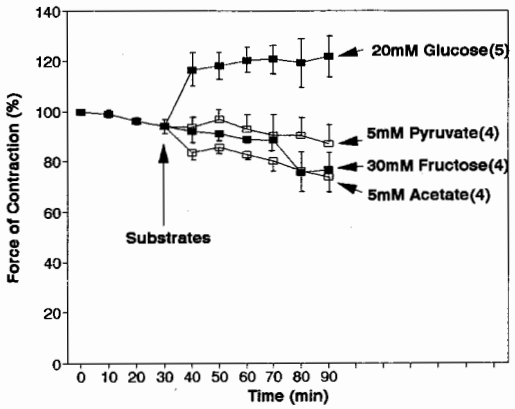

Fig. 3. Effects of substrates on contractility of isolated rat atria in the normal Krebs-Ringer bicarbonate medium containing 5.5 mM glucose. 5 mM pyruvate, 5 mM acetate, 30 mM fructose, and 20 mM glucose were added 30 minutes after the equilibration period in the normal medium. Each value represented as mean±standard error. Parenthese represent number of experiments. Temperature 30°C, pH 7.4.

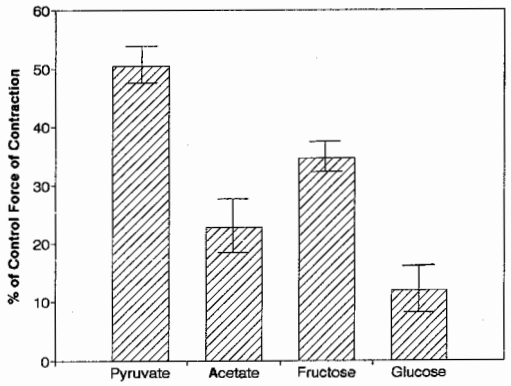

Fig. 5. Ability of substrates to produce a maximal increase in the force of contraction of atria depressed with 0.01 mM bupivacaine. Bar indicate the mean increase in the force of contraction produced by substrates 30 minutes after its addition as a function of its untreated control points. Each value represented as mean±standard error. Temperature 30°C, pH 7.4.

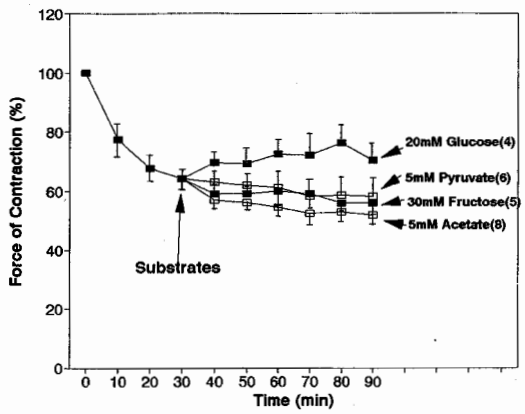

Fig. 4. Effects of substrates on atria depressed with hypertonic medium. In this figure, zero time is that time following a 60 minutes equilibration of the atria in normal Krebs-Ringer medium. 5 mM pyruvate, 5 mM acetate, 30 mM fructose, and 20 mM glucose were added 30 minutes after exposure to hypertonic medium. Each value represented as mean±standard error. Parentheses represent number of experiments. Temperature 30°C, pH 7.4.

chloride to the normal medium, was used rather than bupivacaine to depress the atrial contractility. After 30 minutes of exposure to this medium, the force of contraction stabilized at approximately 65% of the control value (Fig. 4). The addition of 5 mM pyruvate, 5 mM acetate, and 30 mM fructose at this time resulted in no increase in force of contraction (Fig. 4). The contractile force appeared to undergo further depression. These results indicate that depression of the force *per se* is not a sufficient condition to permit pyruvate, acetate, and fructose to effect a recovery in contractility. However, the addition of 20 mM glucose resulted in slight increase in force of contraction (Fig. 4). This result indicates that the glucose metabolism of the heart may not be significantly impaired in the hypertonic medium.

DISCUSSION

Cardiac metabolism has been well studied in recent years, and it has been demonstrated that glucose, pyruvate, fructose, and acetate can be metabolized by the myocardium for the purpose of sustaining the contractile process (Berman and

Saunders, 1955; Gimeno *et al.*, 1969; Ko and Paradise, 1970a, 1970b; Opie *et al.*, 1962; Paradise and Ko, 1970). Exogenous substrates have served as useful tools for the study of cardiac depressant agents. By the use of exogenous substrates, it was previously found that pyruvate, acetate, and fructose partially effective in restoring the contractile activity of isolated rat atria in the hypodynamic state induced by halothane or methoxyflurane (Ko and Paradise, 1969, 1972; Paradise and Ko, 1970) but glucose was no effect on atrial contractility depressed with these inhalation anesthetics. However, it has been reported in the literatures that the additional glucose produce dose-dependent increase in the force of contraction of normal atria (Ko and Paradise, 1973a), whereas the addition of pyruvate and acetate produced only a slight increase in the force of contraction of normal atria, or even acetate produced slight decrease in the contractile activity of the normal atria (Ko and Paradise 1969). From the previous experiments, it was concluded that at least part of negative inotropic effect of halothane or methoxyflurane may be due to the result of inhibition of glucose uptake or blockade of glucose utilization at early step above the PFK step in the glycolytic pathway of the heart.

From the present study, it was found that the metabolic substrate pyruvate, acetate, and fructose partially restored the contractile activity of bupivacaine-depressed atria, whereas additional glucose had no significant effect on the contractile activity of the bupivacaine-depressed atria (Fig. 2). However, additional glucose produced increase in the force of contraction of normal atria(Fig. 3), whereas the addition of pyruvate, acetate, and fructose had no significant effects on the contractility of atria in the normal Krebs-Ringer bicarbonate glucose medium (Fig. 3). These results suggested that pyruvate, acetate, and fructose were utilized by the isolated atria as energy fuel for the contractile process in the presence of bupivacaine, similar to those from the experiments with halothane (Ko and Paradise, 1969, 1970a, 1971b, 1975; Ko *et al.*, 1972) or methoxyflurane (Ko and Paradise, 1972, 1973b), and with substrate-depleted atria (Ko and Paradise, 1970c). It is also suggested that utilization of glucose by the myocardium is impaired in the presence of bupivacaine. And these results are consitent with the previous demonstrations with inhalation anesthetics (Ko and Paradise, 1972, 1973b), barbiturate (Ko, 1981, 1989; Ko and Paik, 1983; Ko and Yoon, 1980), and other local anesthetics (Ko, 1987; Ko *et al.*, 1986; Lim and Kim, 1984).

It has been previously demonstrated that cardiac contractility is depressed by bicarbonate-free medium (Ko and Paradise, 1971d), and these results are consistent with the biochemical data reported by Shaw and Stadie that the bicarbonate-free medium inhibits the PFK activity of diaphragm muscle in the rat (Shaw and Stadie, 1959). It is well established that PFK plays an important role in the regulation of glycolysis in the cell (Shaw and Stadie, 1959), and that the operation of the glycolytic pathway is important for a fraction of the contractile activity of the myocardium (Gimeno *et al.*, 1965; Yang, 1963). It has been reported that neither fructose (30 mM) nor glucose (20 mM) was effective in restoring force of contraction of atria depressed by Krebs-Ringer medium containing 5.5 mM glucose without bicarbonate; however, pyruvate (5 mM) produced a marked positive inotropic effect in the bicarbonate-free medium (Ko and Paradise, 1970b, 1971d). Since bicarbonate is necessary for the PFK activity, these results are taken as evidence that fructose is metabolized via PFK step to serve as an energy-yielding fuel for atrial contractility. Thus, the result further pinpoint the blockade of glucose metabolism by bupivacaine as an early step in the glycolytic sequence prior to PFK step.

It has been reported that no demonstrable effect of the sodium ion can be detected at concentrations below 5 mM (Webb and Hollander, 1956). In the previous report (Ko, 1989), the effect of sodium pyruvate or sodium acetate were due to pyruvate or acetate themself and not due to the sodium ion. The positive inotropic effects of pyruvate, acetate, and fructose on the bupivacaine-depressed atria were again clarified, by using hypertonic medium rather than bupivacaine to depress the atrial contractility, that 5 mM pyruvate, 5 mM acetate, and 30 mM fructose had no effects to restore the depressed atrial contractility in the hypertonic medium. However, 20 mM glucose slightly increased the depressed atrial contractility in hypertonic medium (Fig. 4).

The contractile depression of atria in hypertonic medium is seemed to be related with cytoplasmic calcium concentration (Nakanishi and Jarmakani, 1981), and is not due to the blockade of glucose

metabolism by the hypertonic medium.

It has been demonstrated with rat atria (Gimeno *et al.*, 1965) and rabbit atria (Yang, 1963) that either the uptake of glucose or operation of the glycolytic pathway are important for a fraction of contractile activity since pyruvate is only partially effective in restoring the developed tension in the absence of glucose or during block with 2-deoxy-D-glucose. Similar investigations have been made by Ko and Berman which indicate that pyruvate partially restored the decreased contractility of isolated rat atria (Ko *et al.*, 1969) in phosphate medium either with or without glucose. Pyruvate was relatively effective as an energy source for contaction of isolated rat ventricles in phosphate medium (Berman and Saunders, 1955) and in impaired glucose metabolism in rat heart (Rice and Berman, 1961). From this investigation, the abilities of pyruvate, acetate, fructose, and glucose to produce a maximal increase in the force of contraction of atria in the presence of bupivacaine were compared. Pyruvate has highest ability to elevate the contractile force of bupivacaine-depressed atria (Fig. 5).

The results obtained from this study suggested that bupivacaine blocks the uptake or utilization of glucose via the glycolytic pathway of the heart similar to that of halothane or methoxyflurane, and this blockade must occur above the PFK step in the myocardium, and is at least partly responsible for the negative inotropic action of bupivacaine in isolated rat atria dependent of glucose for their energy supply.

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= 국문초록 =

Bupivacaine에 의해 억제된 심근수축력에 대한 대사기질의 영향

경희대학교 의과대학 약리학교실

박승준 · 정주호 · 정지창 · 고계창

국소마취제인 bupivacaine의 심근억제작용에 관한 기전을 규명하기 위하여, bupivacaine에 의해 수축력이 감소된 흰쥐 적출심장에 대한 각종 대사기질의 영향을 관찰한 바 다음과 같은 결과를 얻었다.

1. Krebs-Ringer glucose medium에 현수한 적출심방의 수축력은 0.01% bupivacaine에 의해 약 50% 감소되었다.

2. Pyruvate, acetate 및 fructose는 bupivacaine 억제심방의 수축력을 증가시켰으나, 정상 Krebs-Ringer medium에서의 수축력에는 현저한 영향이 없었다.

3. Glucose는 bupivacaine 억제심방의 수축력에는 별 영향이 없었으나, 정상 Krebs-Ringer medium에서의 수축력은 증가시켰다.

4. Pyruvate, acetate 및 fructose는 hypertonic medium에 의해 억제된 심방의 수축력에 영향이 없었으나, glucose는 약간의 수축력 증가를 보였다.

5. 각종 대사기질중 pyruvate가 bupivacaine 억제심방의 수축력을 최대로 증가시켰다.

이상의 결과는 bupivacaine이 심근의 glucose 섭취를 억제하거나, 해당과정을 통한 glucose의 이용을 억제하였음을 시사한다. 나아가서, bupivacaine에 의한 대사억제는 심근의 해당과정에서의 phosphofructokinase step이전의 단계에서 작용함을 시사하고 있다.