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Metabolic Properties of Quinidine; Effects of Quinidine Sulfate on Anaerobic Carbohydrate Metabolism of Rat Diaphragm.* (22703)

H. A. ELLS, R. CAPUTTO, AND R. H. FURMAN

Cardiovascular Section, Oklahoma Medical Research Foundation, the Departments of Medicine and Biochemistry, University of Oklahoma School of Medicine, Oklahoma City, and Department of Zoology, University of Oklahoma, Norman

Several papers have appeared recently concerning the effect of quinidine on various aspects of carbohydrate metabolism(1,2,3). The influence of this compound on the anaerobic phase of carbohydrate metabolism has not been thoroughly explored, and results which appear to be conflicting have been reported. Following the work of Furman and Howard(4) confirmed by Fajans and his group(5) who showed that quinidine decreases glucose tolerance in human subjects, we decided to investigate the influence of this drug on the anaerobic metabolism of rat diaphragm in an attempt to gather information on the mechanism of this effect.

The combined results of these experiments on the effect of quinidine on endogenous glycolysis, on glycolysis in the presence of glucose and fructose and on anaerobic consumption of glucose and fructose, point to the conclusion that utilization of these hexoses is impaired at one or more steps close to their entry into the Embden-Meyerhof sequence.

Materials and methods. Albino rats (Holtzman) weighing from 90 to 130 g were used. Following a 24-hour fast the rats were killed by a blow on the head and the diaphragms quickly removed and placed in Krebs-Ringer's bicarbonate solution at 1°C. The diaphragms were cut into either 2 or 4 pieces, weighed and used as soon as possible. All experiments were carried out under anaerobic conditions using the standard Warburg procedure. Incubation was carried out at 37°C in Krebs-Ringer's bicarbonate solution with or without quinidine sulfate (U.S.P., Merck). The flasks were gassed one-half hour with 95% nitrogen-5% carbon dioxide. After an equilibration period of 15 minutes glucose (Baker) or fructose (Nutritional Biochemicals) dissolved in Krebs-Ringer's bicarbonate solution was added from the side bulb to give a final total volume of 3.0 ml. Glucose or fructose was determined by the Somogyi-Nelson method (6).

Results. Effect of quinidine on anaerobic uptake of added glucose and fructose. Glucose (4 mg/ml) and fructose (5 mg/ml) uptake was determined, each in a series of 5 experiments, with or without 1 x 10^{-3} M quinidine. The following mean values and standard errors were obtained: glucose consumption without quinidine, 2.74 ± 0.21 mg/g (wet wt) tissue/hr; with quinidine, 1.44 ± 0.16 mg/g/hr; fructose consumption without quinidine, 2.70 ± 0.27 mg/g/hr; with quinidine, 1.28 ± 0.08 mg/g/hr. The inhibition of glucose or fructose uptake produced by 1 x 10^{-3} M quinidine is significant at the 0.01 level. In 2 experiments in which glucose consumption was measured for a 30-minute pe-

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TABLE I. Effect of Quinidine Sulfate on Anaerobic Glycolysis of Rat Diaphragm. Figures are mean values and ranges for CO_2 production in $\mu l/g$ tissue (wet wt)/hr in Krebs-Ringer's bicarbonate solution. Incubation period 2 hr.

Substrate, mg/ml	No. of exp.	No quinidine		Quinidine concentration	Quinidine		Change in endogenous With quinidine	Stimulation by substrate No quinidine	Stimulation by substrate Quinidine
		Endogenous	With substrate		Endogenous	Substrate		(%)	
Fructose 5	8	100 (77–133)	109 (84–135)	1×10^{-3} M	94 (70–123)	93* (67–106)	− 6	+ 9	− 1
Glucose 1	2	112 (106–118)	162 (155–169)	5×10^{-4} M	105 (99–110)	130 (125–135)	− 6	+ 45	+24
" 1	3	90 (80–99)	132 (108–178)	1×10^{-3} M	88 (83–94)	83 (71–92)	− 3	+ 47	− 6
" 4	2	70 (63–77)	144 (122–167)	1×10^{-3} M	73 (68–77)	78 (75–81)	+4	+106	+ 7

* 5 experiments.

riod the inhibition was less marked: 7.10 mg/g/hr without quinidine; 4.80 mg/g/hr with quinidine.

Effect of quinidine on lactic acid production. The effect of quinidine on the endogenous anaerobic $Q_{CO_2}^{N_2}$ of rat diaphragm and on $Q_{CO_2}^{N_2}$ in the presence of added glucose and fructose is shown in Table I. Endogenous lactic acid production is not affected by 1 x 10^{-3} M quinidine. The results indicate a marked stimulation of lactic acid production by added glucose at concentrations of 1 mg/ml or 4 mg/ml. This stimulation is abolished by 1 x 10^{-3} M quinidine. Quinidine at a concentration of 5 x 10^{-4} only partially inhibits the stimulation of glycolysis by 1 mg/ml of glucose. Added fructose at a concentration of 5 mg/ml produces, unexpectedly, only a slight increase in lactic acid production over the endogenous level. In the presence of added fructose and 1 x 10^{-3} M quinidine, lactic acid production is again reduced to the endogenous level.

Discussion. The experiments reported here show that 1 x 10^{-3} M quinidine inhibits the uptake of added glucose and fructose by rat diaphragm under anaerobic conditions and abolishes the stimulation of glycolysis by glucose and fructose. Endogenous lactic acid production in skeletal muscle has been shown to be at the expense of stored glycogen(7,8). Our observation that quinidine has no effect on endogenous anaerobic glycolysis in intact rat diaphragm suggests that quinidine does not affect any of the metabolic steps between glycogen and lactic acid and therefore inhibits glucose or fructose uptake prior to the step at which these sugars and glycogen share a common metabolic pathway. This suggestion finds support in the work of Uyeki, Geiling and Dubois(3) who found that quinidine did not inhibit lactic acid production from fructose-1, 6-diphosphate in rat heart homogenates.

The inhibitory effect of quinidine on glucose uptake found in the present experiments may account for the decrease in human glucose tolerance noted following quinidine administration(4,5).

Summary. 1. Quinidine sulfate at a concentration of 1 x 10^{-3} M strongly inhibits the uptake of glucose and fructose by intact rat diaphragm under anaerobic conditions. 2. Quinidine is without effect on endogenous anaerobic lactic acid production by rat diaphragm. 3. Glucose at a concentration of 1 mg/ml or 4 mg/ml markedly stimulates anaerobic glycolysis while fructose at a concentration of 5 mg/ml produces only a slight stimulation. 4. Stimulation of glycolysis by glucose or fructose is abolished by 1 x 10^{-3} M quinidine and partially inhibited by 5 x 10^{-4} M quinidine. 5. It is suggested that quinidine inhibits glucose or fructose uptake prior to the step at which these sugars and glycogen share a common metabolic pathway.

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In vitro Effect of Two Pantheine Analogues on Co-Enzyme A Requiring Systems.* (22704)

L. S. DIETRICH AND D. M. SHAPIRO (Introduced by David V. Habif)

Departments of Biochemistry and Surgery, College of Physicians and Surgeons, Columbia University, New York City

The use of metabolic analogues in the study of intermediary metabolism is a method of long standing. That an antagonist of a metabolite active in a multitude of systems would affect each system to varying degrees is predictable in view of the variation in physical constants pertaining to substrate-enzyme, apo-enzyme—co-factor relationships. In the field of vitamin metabolism, experimental data supporting this prediction has only recently been forthcoming(1-4). Analogues have been found which have a very striking antagonizing effect on one or more pathways dependent on the normal metabolite. The same concentration of drug, however, has little effect on other such dependent systems (3,4). These extremes in affinity of metabolic analogues for various systems in which the normal metabolite participates are of great importance in regard to chemotherapy. The present communication extends these observations to analogues affecting pantothenic acid metabolism.

Experimental studies pertaining to the *in vitro* effect of 2 pantethine analogues, omega-methylpantethine and bis (beta-pantoyl-aminoethyl) disulfide on the ability of pigeon liver homogenates to acetylate sulfanilamide and to synthesize citrate from fumarate and pyruvate are presented in the Table. Although omega-methylpantethine inhibited sulfanilamide acetylation, a similar concentration of this compound was without activity against citrate formation. Increasing the concentration of omega-methylpantethine did, however, have some inhibiting effect on the ability of pigeon liver to synthesize citrate from pyruvate and fumarate. The addition of bis (beta-pantoylaminoethyl) disulfide to an aliquot of the same homogenate inhibited citrate formation. At this same concentration little effect was observed on sulfanilamide acetylation. Increasing the level of bis (beta-

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