Species Differences in the Response of Mammalian Myocardial Fatty Acid Metabolism to Quinidine and Disopyramide[1] (34845)

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(Introduced by J. P. LaRocca)

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Although fatty acids are recognized to be important substrates for mammalian myocardial metabolism (1, 2), the influence of cardioactive drugs on lipid metabolism has received relatively little attention. Moreover, species variation of response to antiarrhythmic drugs are poorly known. Quinidine in concentrations of more than 10^{-4} *M* lowers the production of $^{14}CO_2$ from palmitate U-^{14}C in dog heart slices (3) and markedly depresses the myocardial contractile force in cat's papillary muscle preparations (4) and isolated perfused rabbit's heart (5). Gamma-diisopropyl - amino - alpha - phenyl - alpha - (2-pyridyl)-butyramide (disopyramide) is a drug similar to quinidine in that it depresses the myocardial contractile force (5), alters the electrical properties of the myocardial membrane, such as threshold and the rate of rise of the action potential in isolated atrial preparations from rabbit heart (6), and lowers the rate of glucose oxidation and its utilization by the myocardium (7).

The purpose of this investigation is to study the effect of quinidine and disopyramide on oxygen consumption and utilization of palmitate by heart slices from rats, rabbits, and dogs.

Materials and Methods. Adult, male (except as noted), nonfasting animals were used throughout this study. The species were Sprague-Dawley rats weighing 150–280 g, albino New Zealand white rabbits weighing 1.8–3.2 kg, and mongrel dogs (male or female) of 10–12 kg weight.

Standard Warburg manometric techniques were employed for measurement of tissue oxygen consumption as before (7, 8). Rats were decapitated, rabbits were stunned by blows on the head, and dogs were anesthetized with 30 mg/kg of pentobarbital, i.v. The thorax was immediately opened and the heart was removed and placed in buffer at 0–4° without the substrate. Thin (0.5-mm) longitudinal slices were cut from the ventricles with a Stadie-Riggs slicer, halved, and distributed equally between control and drug-containing Warburg reaction vessels which held buffer without substrate. Each vessel received 100–150 mg of tissue. The thermobarometric control vessel contained buffer with substrate, but no drug or tissue. The buffer was that used by Hess and Haugaard (9) and contained 88 m*M* NaCl, 40 m*M* Na_2HPO_4, 5 m*M* KCl, and 2 m*M* $MgCl_2$. The pH of the buffer was adjusted to 7.4 with HCl. The reaction vessels were gassed for 5 min at 37 ± 0.1° and, after initial manometer readings, bovine albumin-bound palmitate (substrate) was added from the side arm. The final concentration of the substrate in the reaction vessel was 0.6–0.8 mg palmitate and 80 mg albumin per 3 ml of reaction mixture. Calculations of Q_{O_2} (μl of oxygen used per mg dry weight per hr) and the chemical determination of free fatty acids (FFA) were made as reported earlier (8).

Fisher's *t* test was used to compare the data of drug-treated animals with that of respective controls and values with $p < .05$ were regarded as significantly different (10).

Results. Table I describes the effects of a

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TABLE I. Effect of Quinidine Sulfate and Disopyramide on Oxygen Consumption and Palmitate Uptake by Heart Slices.

Species, drug	Concentration	Q_{O_2}		Palmitate utilization (μmole/g wet weight/hr)	
		Control[a]	Treated[a]	Control[a]	Treated[a]
Rat, quinidine	1×10^{-6} *M*	5.0 ± 0.22 (4)	4.7 ± 0.13 (4)	1.3 ± 0.06 (4)	1.5 ± 0.07 (4)
	2×10^{-5} *M*	5.5 ± 0.44 (8)	5.5 ± 0.49 (8)	1.5 ± 0.08 (8)	1.1 ± 0.11 (8)[b]
	5×10^{-4} *M*	5.0 ± 0.28 (8)	3.7 ± 0.32 (10)[b]	2.6 ± 0.46 (9)	2.7 ± 0.40 (9)
Rat, disopyramide	1×10^{-6} *M*	5.0 ± 0.22 (4)	4.8 ± 0.19 (4)	1.3 ± 0.06 (4)	1.4 ± 0.05 (4)
	2×10^{-5} *M*	5.5 ± 0.44 (8)	5.4 ± 0.37 (8)	1.5 ± 0.08 (8)	1.1 ± 0.05 (8)[b]
	5×10^{-4} *M*	5.0 ± 0.28 (8)	5.4 ± 0.28 (9)	2.6 ± 0.46 (9)	2.9 ± 0.32 (9)
Rabbit, quinidine	1×10^{-6} *M*	10.9 ± 0.58 (8)	10.1 ± 0.76 (9)	5.1 ± 0.43 (8)	5.9 ± 0.59 (9)
	2×10^{-5} *M*	7.6 ± 0.56 (23)	8.9 ± 1.11 (22)	4.2 ± 0.44 (23)	8.0 ± 0.84 (22)[b]
	5×10^{-5} *M*	7.1 ± 0.66 (16)	7.3 ± 1.05 (17)	4.1 ± 0.68 (16)	7.7 ± 1.45 (17)[b]
	1×10^{-3} *M*	11.2 ± 0.42 (4)	10.0 ± 0.25 (4)	3.5 ± 0.08 (4)	2.5 ± 0.19 (4)[b]
Rabbit, disopyramide	1×10^{-6} *M*	10.9 ± 0.58 (8)	11.4 ± 0.75 (8)	5.1 ± 0.43 (8)	6.2 ± 0.61 (8)
	1×10^{-5} *M*	4.9 ± 0.93 (8)	4.8 ± 1.35 (12)	2.4 ± 1.05 (5)	6.0 ± 0.10 (8)[b]
	1×10^{-4} *M*	6.0 ± 0.74 (18)	6.0 ± 1.13 (20)	2.5 ± 0.47 (15)	4.9 ± 0.50 (16)[b]
	1×10^{-3} *M*	11.2 ± 0.42 (4)	10.7 ± 0.64 (4)	3.5 ± 0.08 (4)	2.7 ± 0.35 (4)
Dog, quinidine	2×10^{-5} *M*	8.7 ± 0.56 (8)	8.4 ± 0.51 (8)	2.7 ± 0.22 (8)	2.7 ± 0.18 (8)
	5×10^{-4} *M*	8.4 ± 0.58 (8)	8.8 ± 0.76 (9)	4.0 ± 0.34 (8)	1.7 ± 0.23 (10)[b]
Dog, disopyramide	2×10^{-5} *M*	8.7 ± 0.56 (8)	9.0 ± 0.60 (8)	2.7 ± 0.22 (8)	3.0 ± 0.33 (8)
	5×10^{-4} *M*	8.4 ± 0.58 (8)	8.2 ± 0.28 (10)	4.0 ± 0.34 (8)	1.1 ± 0.12 (9)[b]

[a] Mean ± SE. Parentheses indicate number of experiments. Each group of experiments was repeated at least four times and for each repetition, heart slices were pooled from four to five rats, two to three rabbits, or one dog.

[b] Significantly different from controls at $p < .05$.

wide range of quinidine and disopyramide concentrations on the oxygen consumption and the uptake of palmitate by heart slices. The drugs did not diminish the oxygen consumption of the tissue slices with the exception of some depression seen at the highest concentration of quinidine in the rat heart. However, some rather remarkable species differences in the rate of disappearance of palmitate were seen. While the rate of disappearance of palmitate from the incubating medium at the higher concentrations of both drugs was significantly depressed in dog heart slices, this effect was slight in rat myocardium and was seen only at drug concentrations of 2×10^{-5} *M*. Rabbit tissue showed a marked increase in palmitate uptake at all except the lowest and highest drug levels; the highest concentration of quinidine (1×10^{-3} *M*) lowered palmitate uptake. Figure 1 illustrates the extent of this phenomenon. The peak increase in palmitate uptake was seen in the dose range of 1×10^{-5} *M* to 5×10^{-5}*M*.

Two other organic bases, which do not exert significant antiarrhythmic effects on the heart *in vitro*, were examined for their influence on palmitate loss from the incubation medium. Atropine sulfate and *N'*-methyl nicotinamide had no significant effect either on palmitate disappearance (Fig. 1) or on Q_{O_2} of the heart slices in the concentrations used.

Discussion. The myocardium uses fatty acids as one type of energy fuel (1, 11). Recently it has also been demonstrated that isolated rabbit heart preparations consume lipids other than phospholipid even in the presence of glucose (12). Palmitic and oleic acids were utilized more rapidly than other fatty acids. In our study, palmitate was supplied as a readily usable exogenous substrate.

Distinct species differences were found in myocardial metabolic responses to quinidine

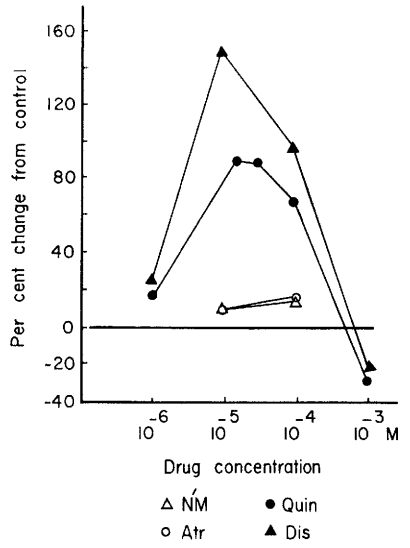

FIG. 1. Change in the loss of palmitate from the incubation medium by rabbit heart slices induced by several organic bases, expressed as per cent change from untreated controls. Quin = quinidine; Dis = disopyramide; N'M = *N'*-methyl nicotinamide; Atr = atropine.

and disopyramide. The differences observed in the rates of palmitate removal from the incubation medium by heart slices of rat, rabbit, and dog in the presence of quinidine and disopyramide are quite obvious. The stability of Q_{O_2} at all concentrations of quinidine and disopyramide in rats, rabbits, and dogs (except that of quinidine at 5×10^{-4} *M* in rats) is remarkable in view of the considerable changes in palmitate removal from the incubation medium. This finding suggests that these agents do not alter the rates of oxidative reactions in the species studied here, at least at the drug concentrations which were tested. The depression of oxygen consumption by the rat myocardium in the presence of quinidine at 5×10^{-4} *M* probably indicated a toxic effect of the drug, but was not observed in rabbit and dog heart slices.

A decrease in the uptake of palmitate by dog heart slices in the presence of 5×10^{-4} *M* quinidine supports the finding of Crevasse and Shipp (3) who demonstrated a lower rate of $^{14}CO_2$ production from palmitate-U-^{14}C in this species. Similar results were obtained in our experiments with disopyramide. It should again be emphasized that these changes in the rates of palmitate uptake were noted without a concomitant change in Q_{O_2} of the myocardial slices.

Rabbit myocardium was unique in the response to quinidine and disopyramide and confirms our previous finding (8) in that there was an increase in the rate of palmitate uptake by the hearts of this animal at drug concentrations of 1×10^{-5} to 1×10^{-4} *M* in the absence of calcium. This effect was not observed at either higher (1×10^{-3} *M*) or lower (1×10^{-6} *M*) concentrations of these drugs. Since there is no simultaneous increase in oxygen consumption of the myocardial slices, this excess palmitate in rabbit heart slices may be entering metabolic reactions other than its oxidation, such as direct incorporation into other lipid fractions of the myocardium.

Summary. The effects of quinidine and disopyramide on oxygen consumption (Q_{O_2}) and palmitate uptake by heart slices of rats, rabbits, and dogs were measured. The drugs did not diminish Q_{O_2} in three animal species studied with the exception of some depression seen at the highest concentration of quinidine in rat hearts. The disappearance of palmitate from the incubation medium was depressed by quinidine and disopyramide at higher concentrations in dogs. Similar depression but of a smaller magnitude was seen in rat myocardium at a lower drug concentration. Rabbit tissue, on the other hand, showed a marked increase in palmitate disappearance from the incubation medium when 1×10^{-5} to 1×10^{-4} *M* concentration of quinidine or disopyramide were tested.

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