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# EFFECTS OF QUINIDINE ON CALCIUM TRANSPORT ACTIVITIES OF THE RABBIT HEART MITOCHONDRIA AND SARCOTUBULAR VESICLES*†

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**Abstract**—The effects of quinidine on the calcium-transporting properties of sarcotubular (heavy microsomal) and mitochondrial fractions of the rabbit heart were investigated and compared with those of procaine amide and lidocaine. High concentrations of quinidine ($10^{-4}$–$10^{-3}$ M) markedly decreased microsomal and mitochondrial calcium uptake; these inhibitory actions were observed at all concentrations of ATP but not when low concentrations of $Mg^{2+}$ were used in the incubation medium. Calcium binding by mitochondrial fraction, unlike microsomal fraction, was also decreased by high concentrations of quinidine. Procaine amide ($10^{-3}$ M) had no effect on microsomal or mitochondrial calcium uptake whereas lidocaine ($10^{-3}$ M) showed a stimulatory action only on the microsomal calcium uptake at initial intervals of incubation. The ATPase activities of both microsomal and mitochondrial fractions were inhibited by quinidine but not by procaine amide or lidocaine. Quinidine, unlike procaine amide and lidocaine, was also found to release about 15% of the calcium bound by microsomes and mitochondria. The results presented in this study suggest that quinidine impairs microsomal and mitochondrial calcium transport; however, other antiarrhythmic agents such as procaine amide and lidocaine, which in high concentrations also depress myocardial contractility, do not decrease calcium transport by heart subcellular particles.

Quinidine in low concentrations has an antiarrhythmic action whereas in high concentrations it is known to depress myocardial contractility and produce contracture of skeletal muscle [1–3]. Many investigators have attempted to explain these pharmacological effects of quinidine on cardiac and skeletal muscles on the basis of its action on calcium transport by sarcoplasmic reticulum [4–8]. It should be pointed out that calcium is generally believed to serve as a link between excitation and contraction of the cardiac and skeletal muscles whereas calcium uptake by sarcoplasmic reticulum is normally associated with muscle relaxation [1, 9–12]. Thus a decrease in sarcoplasmic reticular calcium uptake by quinidine would raise the intracellular level of free calcium and make it more difficult for the muscle to relax. However, unlike skeletal muscle where sarcoplasmic reticulum plays a predominant role in the regulation of intracellular calcium, the calcium movements in cardiac muscle are considered to be regulated by sarcoplasmic reticulum and mitochondria [13–19]. A great deal of further information is therefore required to fully understand the biochemical mechanisms of quinidine on the cardiac muscle.

Although the exact contribution of mitochondrial calcium transport during cardiac contraction and relaxation is controversial [20–22], heart mitochondria like the fragments of sarcoplasmic reticulum (heavy microsomes) are known to accumulate a large amount of calcium under *in vitro* conditions. Therefore it was the purpose of this study to investigate the abilities of both heavy microsomes and mitochondria to transport calcium in the absence and presence of different concentrations of quinidine under various experimental conditions. The actions of quinidine were compared with other antiarrhythmic agents such as procaine amide and lidocaine which are also known to depress myocardial contractility [3].

## METHODS

Healthy male albino rabbits were sacrificed by cervical dislocation, the hearts quickly excised and placed in ice-cold homogenizing medium containing 0.25 M sucrose, 1 mM EDTA and 20 mM Tris–HCl, pH 7.0. Mitochondrial and heavy microsomal fractions were isolated according to procedures described earlier [23]. The purity of the rabbit heart subcellular fractions was assessed and the pattern of their marker enzyme activities and sensitivity to sodium azide was similar to that described earlier for the healthy hamster heart [23]. Both fractions were suspended in 0.25 M sucrose, 10 mM Tris–HCl, pH 7.0 at a protein concentration of 1–2 mg/ml. The protein concentrations were measured by the method of Lowry *et al.* [24]. The procedures for calcium binding and

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uptake by these fractions are similar to those described earlier [23].

Calcium uptake by microsomes was measured in a medium containing 100 mM KCl, 2 mM $MgCl_2$, 20 mM Tris–HCl, pH 6.8–7.0, 2 mM ATP, 5 mM potassium oxalate 0.1 mM $^{45}CaCl_2$. In some experiments 10 mM $MgCl_2$ and 4 mM ATP were also used. The temperature of the incubation medium was 37° and the microsomal protein concentration was 0.02–0.05 mg/ml. Calcium uptake by mitochondria was determined in a medium containing 100 mM KCl, 2 mM $MgCl_2$, 20 mM Tris–HCl, pH 6.8–7.0, 2 mM ATP, 4 mM inorganic phosphate and 5 mM sodium succinate. The mitochondrial protein concentration of 0.1–0.2 mg/ml and an incubation temperature of 37° were used. Calcium binding by mitochondria and microsomes was measured in a medium containing 100 mM KCl, 20 mM Tris–HCl, pH 6.8–7.0, 10 mM $MgCl_2$, 4 mM ATP and 0.1 mM $^{45}CaCl_2$ in a total volume of 1–3 ml. For the binding experiments, mitochondrial protein concentration in the incubation medium at 25° was 0.3–0.4 mg/ml while that of the microsomes was 0.1–0.2 mg/ml. The fractions were preincubated for 3 min in the presence of ATP and drugs, the reactions for binding and uptake were started by the addition of $^{45}CaCl_2$ and stopped by millipore filtration (millipore filter pore size 0.45 μm). The amount of $^{45}Ca$ in 0.1 ml of the protein-free filtrate was analyzed in 10 ml of Bray's solution in a Packard Tri-Carb scintillation spectrometer.

Calcium release by heavy microsomes and mitochondria was determined in the binding medium containing 2 mM $MgCl_2$ and 2 mM ATP. The subcellular particles were preincubated for 10 min at 25° in the presence of 0.1 mM $^{45}CaCl_2$ followed by the addition of drugs. The experimental conditions employed here were such that a maximal amount of calcium was bound to the subcellular particles before initiating its release. The determination of the microsomal and mitochondrial ATPase activities was carried out in a manner similar to that described elsewhere [23] except that the drugs were removed from the solution by treatment with activated charcoal prior to the colour development [4]. The total ATPase activity of the mitochondrial and microsomal fractions (0.1–0.2 mg/ml) was determined in the absence and presence of 5 mM potassium oxalate respectively in a medium containing 100 mM KCl, 20 mM Tris–HCl, pH 6.8–7.0, 2 mM $MgCl_2$, 2 mM ATP and 0.1 mM $CaCl_2$ in a total volume of 2 ml (25°). The basal microsomal ATPase activity was measured in the above medium except $CaCl_2$ was omitted but 0.2 mM EGTA was present. The difference between the total and basal microsomal ATPase activities was referred to as $Ca^{2+}$-stimulated ATPase activity. It should be pointed out that unlike the microsomal fraction, mitochondria do not exhibit $Ca^{2+}$-stimulated ATPase activity under the experimental conditions employed here.

It should be mentioned that calcium binding by subcellular particles is complete within 2–3 minutes. Under the experimental conditions employed in this study to bind calcium for a period of 5 min it was observed that about 50% and 75% of total calcium accumulation occurred in the first minute in the case of mitochondria and sarcoplasmic reticular vesicles respectively. We therefore consider that a part of the bound calcium may be due to uptake within the subcellular particles in our system. It is emphasized that the term 'calcium binding' is applied in this study to indicate calcium accumulation in the subcellular particles in the absence of exogenously added permeant anions and it is understood that this convention employs an arbitrary meaning for binding.

All changes in the experimental conditions are described in the text or indicated under tables and figures. The results were analyzed statistically by the Student *t*-test. All drugs used in the experiments were prepared fresh daily. Quinidine gluconate was obtained from Eli Lilly and Company, Indianopolis, Indiana, procaine amide hydrochloride, from E. R. Squibb and Sons Ltd., Montreal, Quebec and lidocaine hydrochloride, from Astra Chemicals Ltd., Mississauga, Ontario.

## RESULTS

In one series of experiments the effects of quinidine were studied on calcium uptake in the presence of 4 mM ATP and 10 mM $Mg^{2+}$. The effect of various concentrations of quinidine on calcium uptake by heart heavy microsomes and mitochondria are shown in Fig. 1. Quinidine at low concentrations exerted no effect ($P > 0.05$); however, at high concentrations ($10^{-4}$ and $10^{-3}$ M) quinidine significantly ($P < 0.01$) depressed calcium uptake by both heavy microsomes and mitochondria. Calcium binding by heart microsomes and mitochondria was also determined in the presence of various concentrations of quinidine under experimental conditions similar to those employed above for studying calcium uptake except the permeant ions (oxolate for microsomes and Pi for mitochondria) were absent from the incubation medium. The results (Fig. 2) show that microsomal calcium binding remained unaffected over the range of quinidine concentrations tested. However, mitochondrial

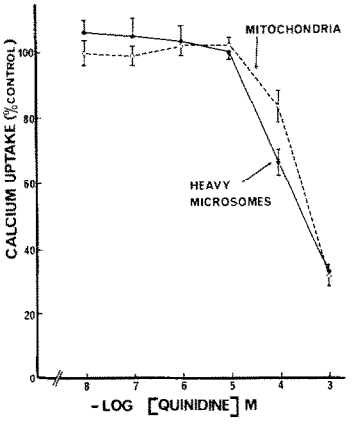


Fig. 1. Effect of various concentrations of quinidine on calcium uptake by rabbit heart heavy microsomes and mitochondria. The incubation medium was the same as described for calcium uptake in the Methods section except that 10 mM $Mg^{2+}$ and 4 mM ATP were used. The time of incubation of the subcellular fractions with $^{45}Ca^{2+}$ was 5 min. The control values for microsomal and mitochondrial calcium uptake were $1342 \pm 162$ and $110 \pm 4$ nmoles/mg protein, respectively. Each value is a mean ± S.E.M. of 5 experiments.

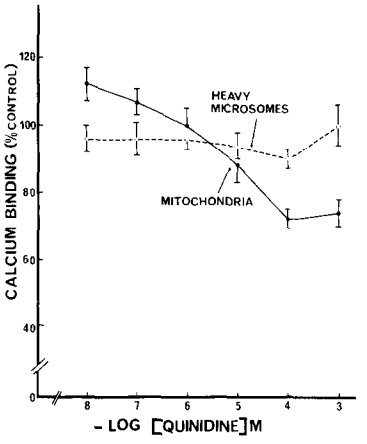


Fig. 2. Effect of various concentrations of quinidine on calcium binding by rabbit heart heavy microsomes and mitochondria. The time of incubation of the subcellular fractions with $^{45}Ca^{2+}$ was 5 min. The control values for microsomal and mitochondrial calcium binding were 49 ± 6 and 43 ± 3 nmoles/mg protein respectively. Each value is a mean ± S.E.M. of 5 experiments.

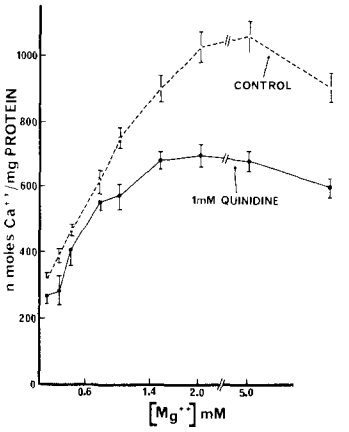


Fig. 3. Influence of $Mg^{2+}$ on the effect of 1 mM quinidine on calcium uptake by rabbit heart heavy microsomes. The incubation medium was the same as that described in the Methods section except various concentrations of $Mg^{2+}$ were employed. The time of incubation of the heavy microsomes with $^{45}Ca^{2+}$ was 5 min. Each value is a mean ± S.E.M. of 5 experiments.

calcium binding was significantly depressed ($P < 0.05$) by $10^{-4}$ and $10^{-3}$ M quinidine. Although quinidine in low concentrations ($10^{-8}$ M) produced a slight stimulation of mitochondrial calcium binding, no effort was made to resolve this point further.

The other set of experiments was carried out to examine the effect of quinidine on calcium uptake in the presence of different concentrations of ATP by keeping the concentration of $Mg^{2+}$ (2 mM) constant as well as in the presence of different concentrations of $Mg^{2+}$ by keeping the concentration of ATP (2 mM) constant. Calcium uptake by heart heavy microsomes and mitochondria in the absence and presence of 1 mM quinidine at various concentrations of ATP is shown in Table 1. Both microsomal and mitochondrial calcium uptake were significantly ($P < 0.05$) reduced in the presence of quinidine at all ATP concentrations tested. The effect of various concentrations of $Mg^{2+}$ on calcium uptake by heart heavy microsomes in the absence and presence of 1 mM quinidine is shown in Fig. 3. At $Mg^{2+}$ concentrations less than 0.75 mM, quinidine exerted no significant effect ($P > 0.05$) on microsomal calcium uptake. At higher concentrations of $Mg^{2+}$ quinidine significantly depressed ($P < 0.05$) calcium accumulation by the microsomal fraction. Preliminary results showed a similar trend of quinidine action on mitochondrial calcium uptake. The results in Table 1 and Fig. 3 with 5 min of incubation in a medium containing 2 mM ATP and 2 mM $Mg^{2+}$ reveal that 1 mM quinidine produced less than 30% inhibition of microsomal calcium uptake whereas it produced more than 60% depression when the incubation medium contained 4 mM ATP and 10 mM $Mg^{2+}$ (Fig. 1). Similar observations were made with mitochondria.

In another series of experiments the effects of quinidine on mitochondrial and microsomal calcium uptake were compared with procaine amide and lidocaine. The time course of calcium uptake by heart heavy microsomes in the presence of 1 mM quinidine.

Table 1. Influence of ATP on the effect of 1 mM quinidine on calcium uptake by heart heavy microsomes and mitochondria

| | Calcium uptake (nmoles/mg protein)* | | | |
|---|---|---|---|---|
| | Heavy microsomes | | Mitochondria | |
| (ATP) mM | Control | Quinidine | Control | Quinidine |
| 0.05 | 563 ± 25 | 394 ± 19† | 85 ± 5 | 63 ± 4† |
| 0.10 | 620 ± 22 | 433 ± 26† | 88 ± 4 | 69 ± 4† |
| 0.50 | 844 ± 30 | 534 ± 20† | 101 ± 4 | 77 ± 5† |
| 1.00 | 1059 ± 32 | 739 ± 35† | 113 ± 6 | 87 ± 4† |
| 2.00 | 1209 ± 42 | 860 ± 44† | 133 ± 5 | 94 ± 5† |
| 5.00 | 440 ± 39 | 322 ± 28† | 91 ± 3 | 67 ± 3† |

* Each value is a mean ± S.E.M. of 5 experiments. The incubation medium was the same as that described for calcium uptake in Methods except that various concentrations of ATP were employed. The incubation time was 5 min.

† Significantly different from the control ($P < 0.05$).

Table 2. Time course of calcium uptake by rabbit heart heavy microsomes in the presence of 1 mM quinidine, procaine amide and lidocaine

| Incubation time | Heavy microsomal calcium uptake (nmoles/mg protein)* | | | |
|---|---|---|---|---|
| | Control | Quinidine | Procaine amide | Lidocaine |
| 30 sec | 355 ± 34 | 457 ± 22 | 476 ± 35 | 675 ± 35† |
| 1 min | 529 ± 37 | 490 ± 21 | 585 ± 38 | 1068 ± 80† |
| 2 min | 813 ± 24 | 586 ± 42† | 718 ± 35 | 1280 ± 102† |
| 5 min | 1272 ± 79 | 698 ± 53† | 1047 ± 70 | 1385 ± 110 |
| 10 min | 1291 ± 85 | 801 ± 45† | 1162 ± 104 | 1414 ± 107 |

* Each value is a mean ± S.E.M. of 6 experiments. The incubation medium was the same as that described for calcium uptake in Methods.
† Significantly different from the control ($P < 0.05$).

procaine amide and lidocaine is shown in Table 2. The depressant action ($P < 0.05$) of quinidine became apparent after 2 min of incubation. Microsomal calcium uptake in the presence of procaine amide (1 mM) was unaffected whereas lidocaine (1 mM) stimulated uptake ($P < 0.05$) during the first 2 min of incubation. The time course of calcium uptake by heart mitochondria in the presence of 1 mM quinidine, procaine amide and lidocaine is shown in Table 3. Mitochondrial calcium uptake was significantly depressed ($P < 0.05$) by quinidine at all time periods during the 10-min incubation whereas procaine amide and lidocaine in concentrations of 1 mM exerted no significant effect on mitochondrial calcium uptake during the course of incubation. Neither procaine amide nor lidocaine in concentrations up to 3 mM had any action on mitochondrial or microsomal calcium uptake when determinations were made by employing 5 min of incubation period.

In order to examine the possibility that the observed depressant effect of quinidine on calcium uptake is a consequence of its interference with active transport process and is not due to release were studied. The data in Table 4 reveal that unlike procaine amide and lidocaine, quinidine (1 mM) decreased microsomal basal and $Ca^{2+}$-stimulated ATPase activity as well as mitochondrial ATPase activity. Quinidine at $10^{-4}$ M concentration also depressed mitochondrial ATPase and microsomal $Ca^{2+}$-stimulated ATPase without affecting the microsomal basal ATPase activity. The depressant effect of quinidine on microsomal and mitochondrial ATPase activities was seen at 2, 5 and 10 min of incubation. The effect of 1 mM quinidine on calcium release by heavy microsomes and mitochondria is shown in Table 5. Five minutes, but not earlier, after the addition of quinidine in the incubation medium containing calcium preloaded microsomal or mitochondrial fractions, a significant ($P < 0.05$) amount (about 15%) of the bound calcium was released. Both procaine amide and lidocaine in concentrations of 1 mM did not induce calcium release from the subcellular particles.

## DISCUSSION

The values for calcium binding and calcium uptake by the mitochondrial and heavy microsomal fractions employed in this study are within the accepted range of values reported by numerous investigators for myocardium from different species. Although there were some differences in values for calcium uptake between two sets of experiments under identical conditions such as those described in Table 1 and Figure 3 for 2 mM ATP and 2 mM $Mg^{2+}$, these slight variations are quite expected in view of the limitations of techniques employed for the isolation of subcellular particles and determination of calcium accumulation. It was for this reason calcium transport by subcellular fractions in the absence or presence of drugs was monitored concomitantly for each set of experiments. Furthermore, it is quite apparent from the results of this study that calcium uptake by mitochondrial and microsomal fractions is dependent upon ATP and $Mg^{2+}$; however, ATP in excess of $Mg^{2+}$ concen-

Table 3. Time course of calcium uptake by rabbit heart mitochondria in the presence of 1 mM quinidine, procaine amide and lidocaine

| Incubation time | Mitochondrial calcium uptake (nmoles/mg protein)* | | | |
|---|---|---|---|---|
| | Control | Quinidine | Procaine amide | Lidocaine |
| 30 sec | 128 ± 4 | 81 ± 3† | 138 ± 6 | 127 ± 6 |
| 1 min | 138 ± 2 | 112 ± 6† | 140 ± 3 | 129 ± 3 |
| 2 min | 155 ± 3 | 125 ± 4† | 143 ± 4 | 156 ± 4 |
| 5 min | 169 ± 5 | 130 ± 5† | 153 ± 3 | 185 ± 7 |
| 10 min | 203 ± 8 | 142 ± 6† | 179 ± 6 | 194 ± 7 |

* Each value is a mean ± S.E.M. of 6 experiments. The incubation medium was the same as that described for calcium uptake in Methods.
† Significantly different from the control ($P < 0.05$).

Table 4. Effect of quinidine, procaine amide and lidocaine on the rabbit heart heavy microsomal and mitochondrial ATPase activities

| | ATPase activity ($\mu$moles Pi/mg protein/hr)* | | |
|---|---|---|---|
| | Heavy microsomes | | Mitochondria |
| | Basal | $Ca^{2+}$-stimulated | Total |
| Control | 34.5 ± 1.0 | 8.5 ± 0.9 | 43 ± 2.0 |
| Quinidine (M) | | | |
| $10^{-7}$ | 34.4 ± 1.3 | 8.6 ± 1.0 | 43 ± 2.0 |
| $10^{-6}$ | 34.5 ± 1.4 | 7.5 ± 1.1 | 43 ± 2.3 |
| $10^{-5}$ | 34.0 ± 1.8 | 7.0 ± 0.8 | 42 ± 2.4 |
| $10^{-4}$ | 33.4 ± 1.1 | 5.2 ± 6.4† | 36 ± 2.5† |
| $10^{-3}$ | 28.0 ± 1.5† | 4.3 ± 6.3† | 25 ± 1.0† |
| Procaine amide | | | |
| $10^{-3}$ M | 35.1 ± 2.2 | 9.2 ± 1.2 | 43 ± 3.1 |
| Lidocaine | | | |
| $10^{-3}$ M | 35.6 ± 1.9 | 8.4 ± 0.8 | 42 ± 2.9 |

* Each value is a mean ± S.E.M. of 5 experiments. The reaction was started by the addition of ATP and was carried out for 10 min. The difference between $Ca^{2+}$-$Mg^{2+}$-ATPase and $Mg^{2+}$ ATPase (basal) activities was taken to be due to $Ca^{2+}$-stimulated ATPase activity.

† Significantly different from the control ($P < 0.05$).

tration in the incubation medium produced marked depressant effects. This inhibitory action of ATP on calcium uptake by the subcellular particles is most probably due to its $Ca^{2+}$ chelating effect, although other membrane effects of free ATP cannot be ruled out.

In this study quinidine has been demonstrated to depress calcium uptake by cardiac heavy microsomes. This is in agreement with the findings of other investigators with both cardiac and skeletal muscle fragments of sarcoplasmic reticulum [4, 6, 7]. The depressant effect of quinidine was apparent at all concentrations of ATP and its magnitude was dependent upon the concentration of $Mg^{2+}$ in the incubation medium. Since the depressant effect of quinidine was not apparent at low concentrations of $Mg^{2+}$, it is likely that quinidine may be acting on the breakdown of a phospho-protein, an intermediate in the transport of calcium [25]. This suggestion is supported by a recently proposed mechanism of quinidine on the inhibition of the cardiac sarcotubule-$\gamma$-$AT^{32}P$ reaction [26].

Table 5. Calcium release from the rabbit heart heavy microsomal and mitochondrial fractions by 1 mM quinidine

| Time after the addition of quinidine | Calcium released (% of the bound calcium)* | |
|---|---|---|
| | Heavy microsomes | Mitochondria |
| 30 sec | 1 ± 0.5 | 2 ± 1.2 |
| 1 min | 5 ± 2.1 | 3 ± 2.5 |
| 2 min | 7 ± 3.6 | 9 ± 3.8 |
| 5 min | 15 ± 3.3† | 13 ± 4.3† |

* Each value is a mean ± S.E.M. of 6 experiments. Both mitochondria and microsomes were loaded with calcium by incubating with 0.1 mM $^{45}CaCl_2$ for 10 min in a medium containing 2 mM ATP and 2 mM $Mg^{2+}$ and were further incubated in the absence or presence of quinidine for different intervals. The differences between calcium values in the absence and presence of the drug were expressed as percent of the steady state values which varied between 66 and 70, and 102 and 114 nmoles $Ca^{2+}$/mg protein for microsomes and mitochondria respectively.

† Significant release ($P < 0.05$).

Since calcium uptake as measured in this study can be considered to be a result of active influx and passive efflux of calcium across the vesicular membranes, the observed decrease in calcium uptake due to quinidine may be a consequence of the action of this drug on these processes. This is substantiated by the results reported in this study as well as from the fact that quinidine has been reported to decrease the activity of microsomal $Ca^{2+}$ stimulated ATPase which is considered to be involved in the active transport of calcium [4, 7]. The slight calcium releasing effect of quinidine may also account partly for the apparent depression in microsomal calcium uptake by this agent, but this component may not be of appreciable significance since permeant ion, oxolate, employed in the incubation medium will minimize calcium efflux by precipitating calcium in the vesicle. The observed depression of calcium uptake by quinidine may not be due to changes in calcium binding ability of cardiac microsomes. This is borne out by our results that in some experiments when calcium uptake was depressed, calcium binding was not altered. Since the effect of quinidine on calcium binding was not studied under all the experimental conditions employed for investigating calcium uptake in this study, our conclusion with respect to ruling out the calcium binding effect should be taken with some caution.

It was demonstrated in this study that quinidine depressed mitochondrial calcium uptake. The depressant effect of quinidine on calcium uptake was apparent at various concentrations of ATP and was $Mg^{2+}$-dependent. It should be noted that concentrations of quinidine which inhibited mitochondrial calcium uptake also decreased calcium binding. Although quinidine also depressed mitochondrial ATPase activity, the relation of this mitochondrial ATPase with calcium transport is not yet clear. On the basis of

the available information concerning mitochondrial calcium transport it is difficult to state with certainty the exact site of drug action and therefore further studies are clearly needed to elucidate this mechanism.

Although it has been shown that quinidine affects the calcium transport properties of sarcoplasmic reticulum and mitochondria, the *in vitro* concentrations that were used to elicit these effects appear to be higher than the doses of this drug which are employed therapeutically for the treatment of common arrhythmias. However, it is possible that the local concentration of the drug at the microsomal and mitochondrial sites may be different than that in the circulation. In this regard it should be noted that quinidine has been shown to bind with sarcoplasmic reticulum and mitochondria [7, 27]. It should be noted that unlike quinidine, other antiarrhythmic agent such as procaine amide was observed to have no effect on microsomal calcium uptake while lidocaine showed an initial stimulatory effect. Shinebourne *et al.* [6] were unable to observe an effect of lidocaine on calcium uptake by cardiac microsomes. Both procaine amide and lidocaine had no influence on mitochondrial calcium uptake. The ATP hydrolyzing activities of both microsomal and mitochondrial fractions were also not altered by procaine amide and lidocaine. Although disturbances in the regulation of intracellular calcium can be conceived to result in irregular cardiac performance, it is unlikely that the observed depression in mitochondrial and microsomal calcium uptake by quinidine has anything to do with its antiarrhythmic action.

Cardiodepressant action of high doses of quinidine has been suggested to be due to its influence on microsomal calcium uptake [4]. Since mitochondrial calcium uptake is also decreased by high concentrations of quinidine, the depression of myocardial contractility by this drug may also be due to its action on mitochondria. Although a time-course effect experiment revealed that calcium uptake by mitochondria was inhibited at 30 sec whereas significant depression in microsomal calcium uptake was apparent at 2 min of incubation with quinidine, the significance of these *in vitro* observations in terms of their *in vivo* effects is far from clear. It should be noted that inhibition of calcium uptake by microsomes [28] and mitochondria [29] by barbiturates has also been reported to explain their cardiodepressant actions. Particularly, a decrease in calcium uptake can be conceived to reduce the intracellular calcium stores and subsequently a less amount of calcium will be available for release from the subcellular membranes upon excitation and this will result in decreasing myocardial contractility by cardiodepressant agents. However, procaine amide and lidocaine which like quinidine are known to produce varying degrees of cardiodepressant action [3] failed to decrease calcium uptake by mitochondria and microsomes. This could mean that the mechanisms of cardiodepressant action of procaine amide and lidocaine are different from that of quinidine. Alternatively, it is possible that the cardiodepressant actions of antiarrhythmic agents are mediated through their influence on sarcolemmal and myofibrillar sites or mitochondrial and sarcoplasmic reticular functions other than calcium transport. Whatever the mechanism of quinidine action may be, the results reported in this paper demonstrate that this agent impairs calcium uptake by both microsomal and mitochondrial fractions of myocardium.

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