Variations in potassium concentration modify the inhibitory effect of lorcinide on myocardial Na^+ - K^+ -ATPase activity

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1 The inhibitory action of lorcinide on the myocardial Na^+ - K^+ -ATPase (EC 3.6.1.3) activity was studied in guinea-pig heart preparations at medium K^+ concentrations of 2.5, 5.0 and 10 mM.

2 Lorcinide exhibited characteristically similar concentration-dependent inhibitory effects at all three K^+ concentrations tested. However, the inhibitory potencies were significantly increased at decreased K^+ concentrations.

3 The IC_{50} values were $10.4 \pm 3.2 \mu\text{M}$ at 2.5 mM, $28.3 \pm 7.9 \mu\text{M}$ at 5.0 mM and $40.7 \pm 9.2 \mu\text{M}$ at 10.0 mM K^+ respectively. Thus, reduction in the K^+ concentration from the 'standard' 5.0 to 2.5 mM enhanced the inhibitory potency of lorcinide, the effective concentrations being shifted towards much lower ranges, while increasing it to 10 mM on the other hand produced opposite but less marked effects.

4 These results show that the inhibition of myocardial Na^+ - K^+ -ATPase activity by lorcinide depends on the K^+ concentration of the incubation medium. These effects are probably related to the mechanism by which lorcinide interferes with the electrogenic Na^+/K^+ pump activity of the enzyme, and hence may contribute to some of its cardiac actions.

Keywords: Lorcinide; potassium; antiarrhythmic agents; Na^+ - K^+ -ATPase

Introduction

The ability of antiarrhythmic drugs to initiate or aggravate existing cardiac arrhythmias has been known for some time. It is only recently however, that the clinical significance of this potential risk of antiarrhythmic drug therapy has been appreciated (Bigger & Sahar, 1987; Morganroth, 1987; Rosen & Wit, 1987; Zipes, 1987). This has been further emphasized by the publication of the preliminary report of the Cardiac Arrhythmia Suppression Trial (CAST) Investigators (1989). Lorcinide, like most antiarrhythmic agents in current use, shares this proarrhythmic property (Podrid *et al.*, 1987; Levine *et al.*, 1989). In a recent study (Almotrefi & Dzimir, 1991a), we have shown that lorcinide is a potent inhibitor of the adenosine 5'-triphosphate (ATP)-hydrolytic action of myocardial Na^+ - K^+ -ATPase. The implication of this finding with regard to the drug's mode of action is not completely clear. It appears likely, however, that this action could be related to proarrhythmic or arrhythmogenic effects of this compound, in a fashion similar to that ascribed to digitalis-induced arrhythmias (Ferrier, 1977; Kass *et al.*, 1978; Smith *et al.*, 1984). Indeed, by virtue of its role in the active transport of monovalent cations across the cardiac cell membrane, Na^+ - K^+ -ATPase is a potential target for disturbances in the initiation and propagation of cardiac action potential which lead to cardiac arrhythmias.

The idea that disturbances in K^+ balance probably interfere with antiarrhythmic drug action is quite old (Holland & Klein, 1958; Rosen, 1971; Goldstein *et al.*, 1973; Obayani *et al.*, 1975). There is also compelling evidence pointing to the fact that low K^+ concentrations potentiate the inhibitory effect of cardiac glycosides on Na^+ - K^+ -ATPase leading to precipitation of cardiac arrhythmias (Klieger *et al.*, 1966; Aaronson & Nordin, 1988). Similarly, disturbance in K^+ balance is also regarded as a risk factor for the development of cardiac arrhythmias in response to class IC antiarrhythmic drugs, such as lorcinide (Morganroth, 1987; Levine *et al.*, 1989). Recently, attempts have been made to elucidate the electrophysiological mechanisms pertaining to the role of low K^+ concentration in the proarrhythmic and arrhythmogenic

effects of antiarrhythmic drugs (Bigger & Sahar, 1987; Woosley & Roden, 1987; Morganroth, 1987). On the other hand, however, little has been published concerning the possible biochemical basis of such interactions. In the present study, we therefore address the question whether variations in K^+ concentration have any influence on the inhibition of myocardial Na^+ - K^+ -ATPase activity by lorcinide and attempt to assess the possible relevance of such interactions to some of its cardiac effects.

Methods

Enzyme preparation

Myocardial Na^+ - K^+ -ATPase was prepared as described previously (Dzimir *et al.*, 1987). Guinea-pigs of either sex weighing 500–800 g were killed by a blow on the head and bled. The heart was removed rapidly and placed in ice-cooled isotonic sucrose buffer (180 mM). Four hearts were minced in a bio-homogenizer (Biospec Products Inc., U.S.A.) and homogenized (Stedfast Stirrer, Fisher Scientific) for 10 min in the sucrose buffer to give a 15% suspension. The homogenate was centrifuged for 15 min at 14000 *g* in a Sorvall RC5C Centrifuge (Sorvall Instruments, U.S.A.), the supernatant filtered through a SC 8.0 μm filter (Millipore Corporation, U.S.A.) and then separated on a TSK Toyopearl Gel HW-55F column (Pierce Chemicals, U.S.A.) equilibrated with KCl buffer (KCl 500 mM, imidazole 10 mM, $\text{Na}_2\text{-EDTA}$ 1 mM, pH 7.4). Ascending elution of the enzyme was carried out at a flow rate of 0.7 ml min⁻¹ maintained by means of a peristaltic pump (LKB Bromma). The fractions were collected using LKB-2211 Superrac and dialysed in 20/32 Visking dialysis membrane (Serva Finebiochemica, USA) three times, each time for at least 6 h, twice with 10 mM first, and then once with 100 mM imidazole buffer, pH 7.4. All steps were carried out at 4°C. The enzyme was stored at the same temperature and could be used for up to five days without appreciable loss of activity. The enzyme preparations were free of mitochondrial particles (Fricke & Klaus, 1974).

Determination of enzyme activity

Enzyme assays were run at 37°C in the presence of different drug concentrations. The drug was pre-incubated at this temperature together with 10–12 μg enzyme (protein) for 20 min in

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100 mM imidazole buffer containing (in mM) Mg^{2+} 5, Na^+ 100, K^+ 5 and $\text{Na}_2\text{-EDTA}$ 1, and the reaction initiated by $2\text{ }\mu\text{M}$ ATP giving a total volume of 1.0 ml. Similar assays were also run in incubation medium containing 2.5 and 10.0 mM K^+ . The effects of lorcinide were tested in the range of 1.0 nM–10.0 mM. The liberated inorganic phosphate was determined spectrophotometrically after 20 min at 660 nm by the method of Eibl & Lands (1969), each assay being performed in duplicate. The $\text{Na}^+\text{-K}^+$ -stimulated ATPase activity was calculated as the difference between the total and the Mg^{2+} plus Na^+ -dependent activity. All results were corrected for blank values without the enzyme. The concentration for half maximal inhibition (IC_{50}) of the $\text{Na}^+\text{-K}^+$ -ATPase were calculated from individual concentration-effect curves as proposed by Hafner *et al.* (1977). Protein concentration of the enzyme preparation was determined by use of Coomassie protein assay reagent (Pierce Chemicals, U.S.A.).

Lorcinide HCl was donated by Janssen Pharmaceutica (Belgium). All the other reagents were of analytical grade. Values are given as mean $\pm$ s.d. Statistical significance was calculated with Student's *t* test (paired to compare drug effects at different K^+ concentrations; unpaired for effects at the same K^+ concentrations) and distribution fitting tests (Kolmogorov-Smirnov and Chi tests to compare the geometrical and normal distribution of the mean values) were carried out with the Statgraphics software package version 3.0 (Graphic Software Systems, 1988). Significance criteria refer to $P < 0.05$.

Results

The initial experiments to study the role of K^+ on the ATP-hydrolytic action of myocardial $\text{Na}^+\text{-K}^+$ -ATPase showed that the enzyme activity increased with increasing K^+ concentration up to approximately 20 mM (Figure 1). Above this concentration, $\text{Na}^+\text{-K}^+$ -ATPase showed no statistically significant change in activity. At all the tested K^+ concentrations, lorcinide exhibited concentration-dependent inhibitory actions on the $\text{Na}^+\text{-K}^+$ -ATPase activity, which also showed similar trends in their concentration-effect relationships. However, as depicted in Figure 2, these inhibitory actions were significantly influenced by varying the K^+ concentration. Thus, under 'standard' (5 mM K^+) conditions, lorcinide exerted its inhibitory effects on the enzyme activity (5–95% inhibition) in the range of 0.13–950 μM , with IC_{50} value of $28.3 \pm 7.9\text{ }\mu\text{M}$. Reduction of the K^+ concentration to 2.5 mM on the other hand shifted the inhibitory concentration-range to 0.01–700 μM , thereby reducing the IC_{50} value to $10.4 \pm 3.2\text{ }\mu\text{M}$, while doubling it to 10.0 mM K^+ shifted the range to 0.3–1300 μM , increasing its IC_{50} value to $40.7 \pm 9.2\text{ }\mu\text{M}$. The corresponding IC_{20} values were

Figure 1 Effect of various K^+ concentrations on myocardial $\text{Na}^+\text{-K}^+$ -ATPase activity expressed as a percentage of total activity observed in the presence of 5 mM K^+ (●) and as a percentage of maximally attainable enzyme activity observed in presence of 20 mM K^+ (▲). Plotted are the mean values of 8 individual determinations; s.d. shown by vertical bars.

Figure 2 Influence of different concentrations of lorcinide in presence of 2.5 (▲), 5.0 mM (●) and 10.0 mM (▼) K^+ on guinea-pig myocardial $\text{Na}^+\text{-K}^+$ -ATPase. The mean enzyme baseline activities (100%) were 22.7 ± 6.2 , 24.2 ± 5.3 and $26.4 \pm 7.4\text{ }\mu\text{M Pi mg}^{-1}\text{ protein h}^{-1}$ at 2.5, 5.0 and 10.0 mM K^+ , respectively. Plotted are the mean values of 7 or 8 individual determinations; s.d. shown by vertical bars.

$21.4 \pm 3.7\text{ nM}$ at 2.5 mM K^+ , $0.9 \pm 0.2\text{ }\mu\text{M}$ at 5.0 mM K^+ and $10.1 \pm 1.7\text{ }\mu\text{M}$ at 10.0 mM K^+ , respectively (Table 1).

Accordingly, reduction of the K^+ concentration by half caused a significant ($P < 0.001$) right-to-left shift in the effective inhibitory concentration range, lorcinide exerting significant actions ($P < 0.05$) at concentrations as low as 10 nM. On the other hand, increase in the K^+ concentration decreased these actions, resulting in a left-to-right shift in effective inhibitory concentration-ranges. These trends are further demonstrated in Figure 3 which compares the changes in enzyme activity at different lorcinide concentrations in relation to the

Table 1 The inhibitory actions of lorcinide on microsomal $\text{Na}^+\text{-K}^+$ -ATPase activity in guinea-pig heart preparations incubated at different K^+ concentrations

K^+ conc. (mM)	n	*IER (μM)	** IC_{20}	*** IC_{50} (μM)
2.5	8	0.01–700	$21.4 \pm 3.7\text{ nM}$	10.4 ± 3.2
5.0	7	0.13–950	$0.9 \pm 0.2\text{ }\mu\text{M}$	28.3 ± 7.9
10.0	8	0.3–1300	$10.1 \pm 1.7\text{ }\mu\text{M}$	40.7 ± 9.2

* The inhibitory effective range, defined as the concentration-range at which the drug inhibits 5–95% of the enzyme activity.

** The concentration required to inhibit the enzyme activity by 20%.

*** The median inhibitory concentration, defined as the concentration required to inhibit the enzyme activity by 50%. IC_{20} and IC_{50} values are expressed as means $\pm$ s.d.

Figure 3 Comparative effects of various incubation medium concentrations of K^+ on the inhibitory actions of lorcinide on guinea-pig myocardial $\text{Na}^+\text{-K}^+$ -ATPase. The relative effects of lorcinide in presence of 2.5 (open columns) and 10.0 mM (solid columns) K^+ are calculated using as baseline the total enzyme activity at standard 5.0 mM K^+ (cross hatched columns). The mean baseline activity of the enzyme at 5.0 mM K^+ was $26.5 \pm 7.8\text{ }\mu\text{M Pi mg}^{-1}\text{ protein h}^{-1}$. The first point represents the relative change in enzyme activity in the absence of lorcinide. Plotted are the mean values of 7–10 individual determinations; s.d. shown by vertical bars.

total activity at the standard (5 mM) K^+ level. As depicted in Figure 3, at 10.0 mM K^+ the enzyme activity remained sustained above that of the standard K^+ concentration up to approximately 50 μM . Lorcaïnide failed to attain 100% inhibition at pharmacologically relevant concentrations. At 2.5 mM K^+ on the other hand, the differences in inhibitory actions became increasingly significant with decreasing lorcaïnide concentrations.

Discussion

The results demonstrate that in the absence of inhibitor, myocardial $\text{Na}^+\text{-K}^+\text{-ATPase}$ activity increased with K^+ concentration, with maximal activity being attained at approximately 20 mM K^+ . A similar influence of K^+ on myocardial $\text{Na}^+\text{-K}^+\text{-ATPase}$ activity has been established previously (see Akera *et al.*, 1979, for review). The present findings confirm the importance of K^+ as a principal determinant of myocardial $\text{Na}^+\text{-K}^+\text{-ATPase}$ activity. The study also shows that in the presence of an inhibitor, such as lorcaïnide, the inhibitory potency is enhanced significantly by reducing the K^+ concentration level of the incubation medium. Thus, although lorcaïnide produces similar concentration-dependent inhibitory effects at the tested K^+ concentrations, variation in the 'standard' K^+ concentration exhibits a profound effect on the sensitivity of the enzyme towards inhibition by the drug. It can therefore be concluded that, while K^+ is required for the $\text{Na}^+\text{-K}^+\text{-ATPase}$ activity, its depletion enhances the inhibition of the enzyme activity by lorcaïnide. Similarly, a reduction in K^+ concentration increases the sensitivity of $\text{Na}^+\text{-K}^+\text{-ATPase}$ inhibition by cardiac glycosides as specific inhibitors of the enzyme (Smith *et al.*, 1984), thereby potentiating their ability to induce cardiac arrhythmias (Aronson & Nordin, 1988). Such interactions of low serum K^+ concentrations with cardiac glycosides have been implicated as important factors in the development of a variety of digitalis-induced arrhythmias (Nordrehaug *et al.*, 1985; Cleland & Dargie, 1988) as well as those induced by antiarrhythmic agents (Levine *et al.*, 1989).

Recently, two plausible suggestions have been made to explain the electrophysiological basis of digitalis-induced arrhythmias (Aronson & Nordin, 1988). Thus, the arrhythmogenic interaction between cardiac glycosides and low K^+ concentration may be a product of the latter enhancing the production of triggered activity by delayed after-depolarizations as a result of its increasing the magnitude of the inward component of the oscillatory current induced by cardiac glycosides. Alternatively, reduced K^+ concentration may decrease the background membrane conductance, thereby increasing the magnitude of the digitalis-induced after-depolarizations, without it affecting the magnitude of the underlying oscillatory current. These after-depolarizations

occur as a result of the steroids interfering with the electrogenic pump activity of the enzyme. Thus, by inhibiting the ATP-hydrolytic action of the enzyme, the cardiac glycosides impede the electrogenic pumping of Na^+ out and K^+ into the cell, which interferes with the restoration of resting potential. This may in turn cause after-depolarizations which may trigger arrhythmias (Ferrier, 1977). Class IC antiarrhythmic agents such as lorcaïnide can trigger early after-depolarizations (Levine *et al.*, 1989). Such secondary depolarizations may also result from low extracellular K^+ . It remains to be established whether such electrical disturbances occur as a product of malfunction of the electrogenic pump activity triggered by the inhibition of the ATP-hydrolytic action of myocardial $\text{Na}^+\text{-K}^+\text{-ATPase}$ by lorcaïnide. Nevertheless, based on the currently available information, it seems reasonable to postulate a relationship between the inhibitory actions of antiarrhythmic drugs on myocardial $\text{Na}^+\text{-K}^+\text{-ATPase}$ and the mechanism of their pro-arrhythmic or arrhythmogenic effects. There were several observations which support such a hypothesis. To begin with, the ability to induce or enhance already existing arrhythmias is a property shown by most of the currently available antiarrhythmic drugs, including lorcaïnide (Woosley & Roden, 1987; Zipes, 1987). According to recent suggestions, such arrhythmias may be caused, in part at least, by disturbances in ionic balance, particularly that of K^+ and Na^+ (Rosen & Wit, 1987; Bigger & Sahar, 1987; Levine *et al.*, 1989), which may in turn occur as a result of the inhibition of the electrogenic pump activity of $\text{Na}^+\text{-K}^+\text{-ATPase}$ in a fashion similar to that which triggers the digitalis-induced arrhythmias (Ferrier, 1977). It is also well-established that, apart from lorcaïnide, several other antiarrhythmic agents are also potent inhibitors of $\text{Na}^+\text{-K}^+\text{-ATPase}$ activity (Goldstein *et al.*, 1973; Cook *et al.*, 1983; Prasada Rao *et al.*, 1986; Aomine, 1989; Almotrefi & Dzimir, 1990; 1991b; Dzimir & Almotrefi, 1990). Likewise, it appears that the reduction in K^+ concentrations also enhances the inhibitory actions of other antiarrhythmic drugs, such as amiodarone, for example (Dzimir & Almotrefi, 1991).

Therefore, all the above observations seem to point towards a common mechanism for some of the cardiac actions shared by antiarrhythmic drugs and cardiac glycosides, such as their ability to induce cardiac arrhythmias. The present findings also suggest that changes in myocardial K^+ concentration may affect the responsiveness of $\text{Na}^+\text{-K}^+\text{-ATPase}$ towards inhibition by lorcaïnide. If the hypothesis implicating the inhibition of $\text{Na}^+\text{-K}^+\text{-ATPase}$ activity in the pro-arrhythmic and arrhythmogenic actions of lorcaïnide is correct, these findings further indicate that hypokalemia may result in aggravation of these arrhythmias during treatment with lorcaïnide.

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