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Interaction of amrinone with endogenous adenosine in guinea-pig atria

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1 In spontaneously beating atria from reserpine-treated guinea-pigs, amrinone (10 μM to 2 mM) induced a positive inotropic and chronotropic effect that was preceded by a transient reduction in contractile force and in frequency. Both the positive and negative effects were concentration-dependent.

2 The inotropic action of amrinone was antagonized by low concentrations of 8-phenyltheophylline that compete with adenosine at R-receptors on plasma membrane without significantly influencing phosphodiesterase activity.

3 Cumulative concentrations of amrinone (1 mM) antagonized the reduction of rate of contraction and amplitude induced by dipyridamole 1 μM in spontaneously beating atria and restored the maximum contractile effect reached in the absence of dipyridamole.

4 In spontaneously beating preparations incubated in the presence of adenosine deaminase (1u ml^{-1}), amrinone lost its positive effects on the atria and only reduction of rate and contractile force was evident. Both effects were antagonized by scopolamine 1 mM thus indicating their cholinergic nature.

5 Adenosine at 0.1 μM and 0.5 μM significantly inhibited the inotropic effect induced by amrinone (0.03 to 3 mM) and the concentration-effect curves of amrinone obtained in the absence and presence of adenosine clearly indicate a competitive antagonism between the two drugs. Thus the contractile activity of amrinone in spontaneously beating atria from reserpine-treated guinea-pigs originates from a displacement of adenosine from its R-receptor sites in the cardiac cell.

Introduction

Amrinone (5-amino-3,4-bipyridin-6(1H)-one; Win 40680) decreases peripheral vascular resistance and increases cardiac output and contractility in a variety of *in vitro* and *in vivo* preparations (Benotti *et al.*, 1978; Alousi & Farah, 1978; Alousi *et al.*, 1979; LeJemtel *et al.*, 1979; Klein *et al.*, 1981; Ward *et al.*, 1983; Toda *et al.*, 1984).

The mechanism of action of amrinone has not been established. The cardiotonic effect is not blocked by β-adrenoceptor blocking agents or by treatment with reserpine (Alousi *et al.*, 1979); unlike cardiac glycosides, amrinone does not inhibit Na^+-K^+ATP-ase activity (Alousi & Farah, 1978; Alousi *et al.*, 1979). Its mode of action in the heart has been related to a direct influence on myocardial contractile elements (Alousi & Farah, 1978) or to alterations in extracellular and intracellular calcium balance (Gaide *et al.*, 1980; Morgan *et al.*, 1980; Azari & Huxtable, 1980; Rending & Amsterdam, 1984) probably mediated by an increased level of tissue cyclic adenosine monophosphate and inhibition of phosphodiesterase (Honerjäger & Schafer-Korting Reiter, 1981; Endoh *et al.*, 1982). Amrinone is in fact particularly effective as an inhibitor of a membrane-bound fraction of phosphodiesterase (Karyia *et al.*, 1982). On the other hand studies in cat, dog and guinea-pig ventricular muscle revealed a positive inotropic effect of amrinone associated with enhanced relaxation (Honerjäger & Schafer-Korting Reiter, 1981; Gaide *et al.*, 1981; Endoh *et al.*, 1982) and in cat ventricle the relaxing effect was primarily manifest as a decrease in contractile force (Karyia *et al.*, 1982). Recently Gaide *et al.* (1983) demonstrated the amrinone relaxant effects in heart muscle taken from cats with pressure overload-induced right ventricular failure and suggested that the primary effect of amrinone in the failing heart may be to enhance myocardial relaxation with secondary increase in cardiac contractility, either

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through an increased coronary blood flow or through improved filling. It is well known in fact that heart failure is associated with impaired relaxation and reduced ventricular compliance (Grossman *et al.*, 1979). In patients with chronic congestive heart failure also the vasodilator action may contribute to the beneficial effects of this inotropic agent (Meisheri *et al.*, 1980). It has been proposed that the vasodilatation originates from a non-specific inhibition of smooth muscle contractility by an action at multiple sites, causing a decrease of calcium availability to the contractile proteins (Grossman *et al.*, 1979). Also in this mechanism variations in cyclic AMP levels may be involved (Meisheri *et al.*, 1980). The opportunity of a search for orally active, more potent and less toxic inotropic agents than cardiac glycosides led us to define more clearly the mechanism of action of amrinone in the heart.

Methods

Isolated atria preparations

Male guinea-pigs (300–500 g) were killed by a blow to the head followed by exsanguination and the atria were separated from the ventricles and suspended vertically in a bath containing 30 ml of physiological salt solution of the following composition (mmol l^{-1}): NaCl 120, KCl 2.7, $MgCl_2$ 0.9, NaH_2PO_4 0.4, $CaCl_2$ 1.37, $NaHCO_3$ 11.9, glucose 5.5. The solution was maintained at 29°C and was bubbled vigorously with a mixture of 95% O_2 and 5% CO_2 which produced a pH of 7.5. Resting tension was adjusted at 1.0 g and developed tension was recorded isometrically through a high sensitivity transducer (Basile Type DYO for isolated auricle) and registered by a writing oscillograph (Basile, Unirecord system, Mod. 7050).

Experimental protocol

The experiments were performed on spontaneously beating atria obtained from reserpine-treated animals. Reserpine (2 mg kg^{-1}, i.p.) was given at 48 and 12 h before the animals were killed in order to eliminate the influence of noradrenaline which might be released from sympathetic nerve terminals (Temma *et al.*, 1977). Noradrenaline depletion was determined by exposing isolated atria to a single dose of tyramine (2 μg ml^{-1}) before starting the experiments. The drugs were added to the perfusion fluid after 90 min of equilibration. Amrinone was added to the medium in a single dose (Figures 1 and 4, Table 1) or in cumulative doses (Figures 2, 3) and the inotropic effect was recorded for 5 min after it reached its maximum before washing or before adding a higher concentration. Where indicated, 8-phenyltheophylline, dipyridamole or adenosine deaminase were added to the perfusion fluid 10 min before amrinone.

The agents that we investigated, and their sources of supply, were as follows: amrinone (Schiapparelli), adenosine deaminase, dypiridamole, scopolamine hydrochloride (Sigma), 8-phenyltheophylline (Calbiochem-Behring). All other chemicals and reagents were of analytical grade.

Results

Effect of amrinone on spontaneously beating atria

In spontaneously beating atria (Figure 1) amrinone, in a concentration range from 10 μM to 2 mM, caused a progressive increase of contractile tension. The increase by amrinone never exceeded 67–70% (Figure 1) of the absolute initial control (tension magnitude after equilibration period). Also the frequency was increased by the drug in a concentration-dependent manner (Figure 1), but this effect was weaker than the influence on contractile force. The positive inotropic and chronotropic effects exerted by amrinone at 1 mM and 2 mM were preceded by a transient, concentration-dependent decrease both in the contractile tension and in frequency rate (Figure 1).

Effect of 8-phenyltheophylline on amrinone-induced inotropic effect

In these experiments 8-phenyltheophylline was used as a potent adenosine antagonist (Burns, 1981; Smellie *et al.*, 1979) lacking significant influence on phosphodiesterase activity in different tissues (Smellie *et al.*, 1979; Dunwiddie *et al.*, 1981; Scotini *et al.*, 1983).

8-Phenyltheophylline induced a progressive increase of contractile tension that corresponded well quantitatively to that induced by amrinone in a concentration range from 10 μM to 1 mM (Table 1). Moreover, when amrinone was added to the medium after 8-phenyltheophyline had reached its maximum effect, the inotropic effect of amrinone was significantly inhibited by the alkylxanthine, but in each assay the presence of both 8-phenyltheophylline and amrinone caused an increment in developed tension responsing well to that induced by amrinone alone (Table 1).

Effect of amrinone on the negative inotropic effect of dipyridamole

In the presence of dipyridamole (1 μM), an inhibitor of adenosine uptake and metabolism, the spontaneously developed tension was markedly reduced (– 74% of the intial control) (Figure 2), but the addition of amrinone to the perfusion medium in cumulative concentrations practically restored the maximum con-

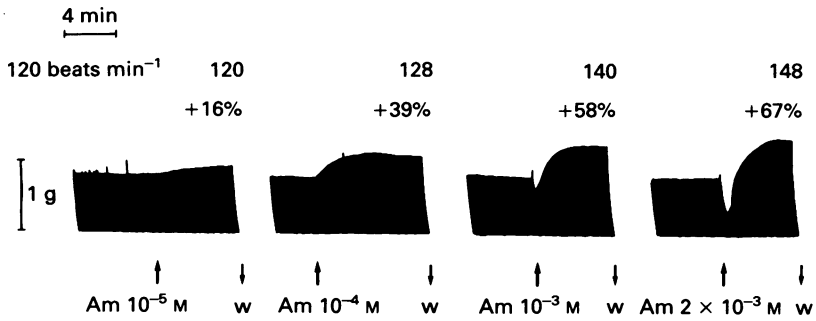

Figure 1 Effect of amrinone on guinea-pig isolated atria. Am = amrinone; + . . . % = increase in isometric tension over control. The tracing is representative of eight experiments on eight preparations.

Table 1 Effect of 8-phenyltheophylline on inotropic activity of amrinone in spontaneously beating atria from reserpine-treated guinea-pigs

		Isometric tension (% increase over control)			
8-Phenyltheophylline		*Amrinone* (M)			
(M)	0	10^{-5}	10^{-4}	5×10^{-4}	10^{-3}
0	—	5.86 ± 0.61	14.02 ± 0.45	25.75 ± 2.62	33.72 ± 3.02
5×10^{-7}	5.98 ± 2.01	0.00	6.14 ± 1.39	19.46 ± 1.96	27.02 ± 2.60
		$P < 0.001$	$P < 0.001$	$P < 0.05$	$P < 0.05$
10^{-6}	13.35 ± 2.21	0.00	0.00	12.65 ± 2.13	21.33 ± 1.97
		$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.005$
5×10^{-6}	24.19 ± 2.60	0.00	0.00	3.20 ± 1.01	11.13 ± 0.93
		$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$
10^{-5}	30.60 ± 3.01	0.00	0.00	0.99 ± 0.09	3.66 ± 0.45
		$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$

Amrinone was added to the medium when 8-phenyltheophylline had reached its maximum effect.
Each result is mean ± s.e. of four to seven assays from seven different experiments with seven animals (at last four experiments for each point). The *P* values were calculated vs respective controls (atria treated with amrinone alone). The statistical significance of the changes induced by 8-phenyltheophylline was calculated by Student's *t* test.

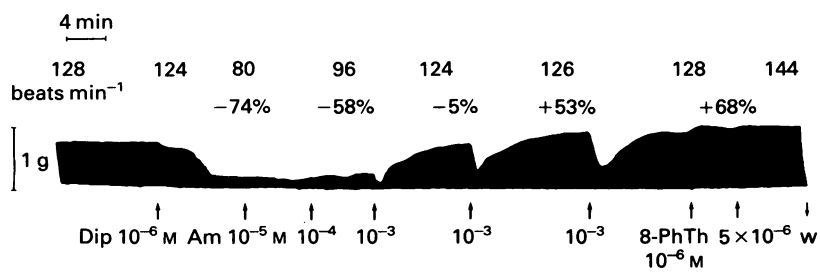

Figure 2 Effect of amrinone and 8-phenyltheophylline on dipyridamole-treated guinea-pig atria. Dip = dipyridamole; Am = amrinone; 8-PhTh = 8-phenyltheophylline. Amrinone and 8-phenyltheophylline were added to the perfusion medium in cumulative concentrations. + . . . % = increase in isometric tension over control. The tracing is representative of four experiments on four preparations.

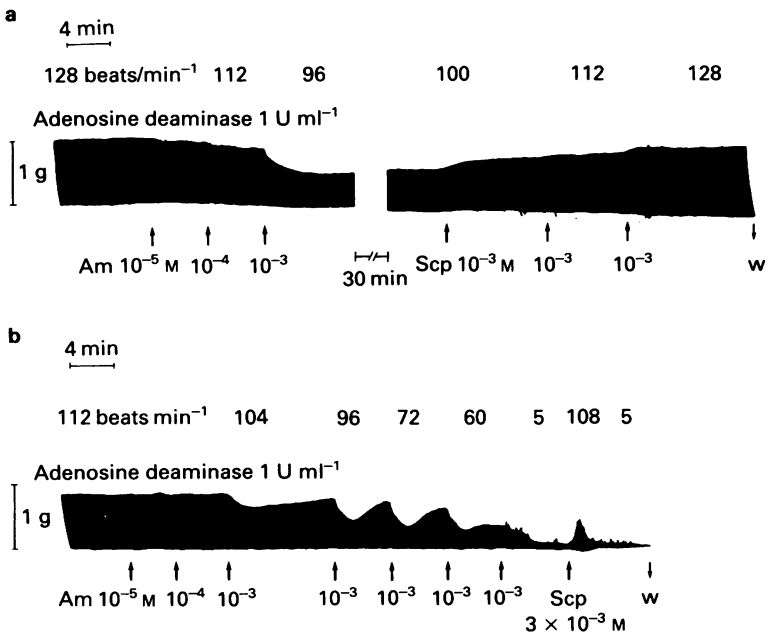

Figure 3 Effect of amrinone on adenosine deaminase-treated guinea-pig atria. Am = amrinone; Scp = scopolamine. Amrinone was added in cumulative concentrations to the perfusion medium of guinea-pig isolated atria preincubated for 10 min with adenosine deaminase (1u ml^{-1}). The tracing is representative of five experiments on five preparations.

tractile activity reached in the absence of dipyridamole and further addition of 8-phenyltheophylline caused only a transient, marginal increase in developed tension and frequency.

Effect of amrinone on spontaneously beating atria incubated in the presence of adenosine-deaminase

In spontaneously beating atria perfused with a medium containing adenosine deaminase (1u ml^{-1}) the cumulative addition of amrinone in concentrations of 10 μM, 0.1 mM and 1 mM did not increase the developed tension or the frequency rate, while the negative influence of the drug on both these parameters was maintained (Figure 3). Under these conditions, scopolamine (3 mM) added in cumulative concentrations restored the frequency rate and the developed tension to the basal levels (Figure 3a). However, multiple additions of amrinone to reach the final concentration of 5 mM suppressed the heart beat, and this was no longer restored by scopolamine (3 mM), thus emphasizing the irreversible nature of the negative influence of amrinone on the atria (Figure 3b).

Adenosine-amrinone interaction in guinea-pig spontaneously beating atria

Pretreatment of spontaneously beating atria with 0.1 μM and 0.5 μM adenosine significantly inhibited the inotropic effect induced by different amrinone concentrations (0.03 to 3 mM). However, the same maximum inotropic effect induced by 3 mM amrinone was still reached in the presence of adenosine 0.1 μM and 0.5 μM by increasing amrinone concentration to 40 mM and 0.3 M, respectively. The concentration-effect curves for amrinone in the presence of adenosine indicate a competitive antagonism between these two drugs (Figure 4).

Discussion

Amrinone, a recently synthesized cardiotonic drug, was found to exert a positive inotropic action that is achieved without apparent cardiac toxicity both in normal human volunteers (De Guzman *et al.*, 1978) and in patients with severe congestive heart failure (Benotti *et al.*, 1978). Even at high doses it does not produce arrhythmias (Alousi & Farah, 1978).

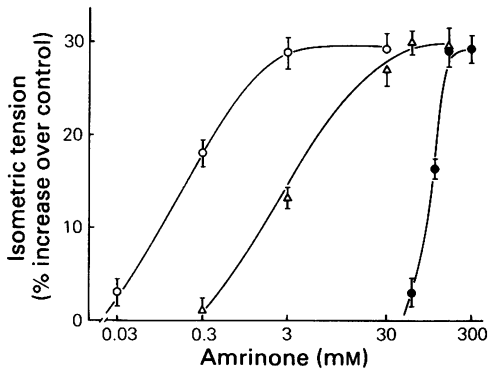

Figure 4 Amrinone-adenosine interaction in guinea-pig isolated atria. (○) Amrinone; (△) amrinone plus 0.1 μM adenosine; (●) amrinone plus 0.5 μM adenosine. Each point is mean of three to six assays from six different experiments with six animals; s.e. shown by vertical lines.

However, in some animal species such as 0 to 4 day-old beagles (Binah *et al.*, 1983) or in Langendorff-perfused isolated heart of the rat (Azari & Huxtable, 1980) amrinone induces a negative inotropic effect. Moreover the positive contractile influence induced by the drug differs in several stimulated isolated cardiac preparations, the order of potencies being: cat papillary muscle > rabbit papillary muscle > guinea-pig left atria (Siegl *et al.*, 1984). Its mechanism of action appears to be novel as it does not involve effects on β-adrenoceptors or Na^+,K^+ ATPase (Alousi & Farah, 1978; Alousi *et al.*, 1979). A direct action on the myocardial contractile process (Alousi & Farah, 1978; Gaide *et al.*, 1980; Azari & Huxtable, 1980) or an inhibition of phosphodiesterase (Honerjäger & Schafer-Korting Reiter, 1981; Endoh *et al.*, 1982; Karyia *et al.*, 1982) have also been claimed as responsible for the inotropic action of amrinone on the heart. Our results clearly indicate that in spontaneously beating isolated atria from reserpine-treated guinea-pigs, amrinone exerts a dual action, i.e. a transient but concentration-dependent negative chronotropic and inotropic effect followed by a net increase both in frequency and in developed tension. The contractile effect induced by amrinone in a range of concentrations from 10 μM to 2 mM corresponded well with the inotropic influence exerted by 8-phenyltheophylline which competes with adenosine at R-receptors on plasma membrane (Smellie *et al.*, 1979; Burns, 1981) without exerting any significant effect on phosphodiesterase activity (Smellie *et al.*, 1979; Dunwiddie *et al.*, 1981; Scotini, 1983). Moreover 8-phenyltheophylline clearly antagonized the amrinone action on developed tension but the further addition of amrinone when 8-phenyltheophylline had reached its maximum effect resulted in an increase of developed tension to the level previously observed in the presence of amrinone alone. In no case did the alkylxanthine potentiate the amrinone contractile effect. This, in accordance with data of Carpenedo *et al.* (1984), excludes any significant involvement of an action on phosphodiesterase in the cardiac effects of amrinone.

We studied the effect of amrinone in the presence of dipyridamole, an inhibitor of adenosine uptake and metabolism and in the presence of adenosine deaminase, the enzyme that inactivates adenosine by metabolizing it to inosine. Amrinone antagonized the dipyridamole-induced decrease in developed tension. Moreover, in these experimental conditions, cumulative additions of amrinone restored the developed tension approximately to the maximum level previously seen with amrinone alone. At this point further additions of 8-phenyltheophylline did not allow further increase in the contractile force of the atria. In spontaneously beating atria incubated in the presence of adenosine deaminase, amrinone (3 mM) had only a negative effect on frequency and contractile force. Both effects were completely abolished by scopolamine, thus indicating that this negative influence of amrinone on guinea-pig isolated atria is cholinergic in nature. However, when a higher amrinone concentration was reached (5 mM) scopolamine did not restore the spontaneous frequency or the spontaneous contractile activity and the atria ceased to beat. These data underline that the cholinergic component of the action of amrinone on the heart becomes irreversible at high drug concentrations and may suggest the possibility of toxicity in particular pathological conditions in human patients. It remains uncertain whether this action of amrinone is a consequence of a direct influence of the drug on cholinergic nervous structures or on muscarinic receptors in the heart. However, more problematic is the fact that adenosine deaminase under our experimental conditions did not have a positive inotropic action on isolated atria. One explanation is that the enzymatic inactivation of endogenous adenosine may activate some compensatory mechanism such as vagal activity to maintain the inotropism at the basal value. Alternatively, products of adenosine metabolism that accumulate during adenosine deaminase treatment may exert a negative action on heart contractility that neutralizes the expected positive effect of the enzyme.

Finally, to substantiate the relation between amrinone and endogenous adenosine, the amrinone contractile effect was studied in spontaneously beating atria incubated with 0.1 μM and 0.5 μM adenosine. Amrinone antagonized the negative inotropic influence exerted by adenosine on the guinea-pig atria and Figure 4 shows the competitive nature of the amrinone-adenosine interaction. These results, together with data obtained in the presence of 8-phenyltheo-

phylline, indicate that the contractile response evoked by amrinone seems to originate from competition with adenosine for its R-receptors in the guinea-pig atria. Since adenosine accumulation in tissue is increased by anoxia, the relatively low increase in developed tension induced by amrinone in the present experiments may be related to the fact that our atria preparations were well oxygenated. If the interaction with adenosine accounts for the action of amrinone in the heart, then the myocardial levels of endogenous adenosine may also explain the differences in the inotropic responses to the drug found among heart muscle preparations from different animal species (Siegl *et al.*, 1984). It must be stressed that in intact animals neither the negative inotropic effect nor catecholamine antagonism of adenosine has been detected so far (Seitelberger *et al.*, 1984). Thus no conclusions can be drawn from the present results concerning the action of amrinone *in vivo*. The observed inotropic effect induced by this drug *in vitro* may be of no physiological importance *in vivo*, in animals or in man.

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