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Effects of α-adrenoceptor agonists and antagonists on ouabain-induced arrhythmias and cardiac arrest in guinea-pig

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1 Effects of α-adrenoceptor agonists and antagonists with different affinity for α_1- and α_2-receptors on ouabain-induced arrhythmias in guinea-pigs were studied.

2 Early arrhythmias, ventricular fibrillation and cardiac arrest were induced in anaesthetized guinea-pigs by the slow intravenous infusion of ouabain.

3 Phenylephrine and yohimbine potentiated the cardiotoxicity of ouabain significantly whereas prazosin and clonidine showed significant antiarrhythmic effects and delayed the cardiac arrest.

4 It is concluded that selective α_1-receptor stimulation and α_2-receptor blockade increases the cardiotoxic effects of ouabain and selective α_2-receptor stimulation and α_1-receptor blockade inhibits ouabain-induced arrhythmias and cardiac arrest in guinea-pigs.

Introduction

Prevention and suppression of some experimental arrhythmias by α-adrenoceptor blocking drugs have long been known (Moe *et al.*, 1948; Nickerson & Nomaguchi, 1949). However, the effects of α-adrenoceptor agonists and antagonists on cardiac arrhythmias induced by cardiac glycosides have not yet been thoroughly investigated. There have been conflicting reports concerning the effect of α-adrenoceptor blocking agents on the arrhythmogenic effects of cardiac glycosides in different experimental animals. Both protection (Ettinger *et al.*, 1969; Gould *et al.*, 1969; Rothans & Powell, 1975) or no effect (Erlig & Mendez, 1964; Melville *et al.*, 1970; Mukherjee *et al.*, 1972) were reported.

The effects of selective α_1- and α_2-adrenoceptor agonists and antagonists on the myocardial toxicity induced by cardiac glycosides have only been partially investigated. It has been demonstrated that selective α_2-receptor stimulation and α_1-receptor blockade protect against ventricular arrhythmias induced by ouabain (Lechat & Schmitt, 1982).

Taking these findings into consideration, the present investigation was undertaken to study the effect of several α-adrenoceptor agonists and antagonists with different affinity for the α_1- and α_2-receptors on the various stages of arrhythmia and cardiac arrest following infusion of ouabain in guinea-pigs.

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Methods

Studies were carried out in albino guinea-pigs of either sex weighing between 350–450 g. The method described by Sekiya & Vaughan Williams (1963) was used with some modification. The animals were anaesthetized with an intraperitoneal injection of pentobarbitone sodium (50 mg kg^{-1}). The trachea was cannulated and a positive pressure artificial respiration was maintained throughout the experiment by means of a rodent respirator (Harvard Apparatus, England) at the rate of 45 strokes per min and volume was adjusted at 1.0 ml 100 g^{-1} body weight. The right jugular vein was cannulated with a polythene tube and connected to a slow injection apparatus for ouabain infusion. The left common carotid artery was cannulated and connected to a Bentley-Trantec physiological pressure transducer and the blood pressure was recorded on a Gemini Recorder (Ugo Basile, Model 7070). Limb lead II ECG was recorded on a Grass Polygraph (Model 7 D) and heart rate was calculated from ECG signals. Ouabain solution (80 μg ml^{-1}) was continuously infused at the rate of 100 μl min^{-1}. The amount of ouabain, required per 100 g body weight, for the onset of early arrhythmia (indicated by the appearance of ectopic beats, prolonged P–R intervals and P waves not followed by QRS

wave), ventricular fibrillation and cardiac arrest was determined in control and drug-treated animals.

Drugs

The drugs used in these experiments were: prazosin hydrochloride (Pfizer), yohimbine hydrochloride (Sigma), phenoxybenzamine hydrochloride (Ferak-Berlin), phenylephrine hydrochloride (Wilson) and clonidine hydrochloride (Cipla). All the drugs were administered i.p. 15 min before ouabain infusion in order to avoid the hypotensive action of some of the agents which might have interfered with the results (Mukherjee *et al.*, 1970).

Statistical analysis

The results were experessed as mean ± s.e.mean and were statistically analysed using Student's *t* test.

Results

The basal blood pressure of guinea-pigs anaesthetized with pentobarbitone sodium was 42.00 ± 3.00 mmHg and the heart rate was 268 ± 7 beats per min. Phenylephrine and yohimbine resulted in an increase in blood pressure which was 56.00 ± 11.34 mmHg and 18.57 ± 1.43 mmHg respectively. Yohimbine also produced a rise in heart rate. All the other drugs used in this study produced a fall in blood pressure and reduction in heart rate (Table 1). These effects particularly on the blood pressure returned to basal level in about 15 min.

Ouabain infused intravenously in guinea-pigs caused early arrhythmia, ventricular fibrillation and cardiac arrest in all control and drug-treated guinea-pigs. The amounts of ouabain required to produce the arrhythmic stages and cardiac arrest in control and treated guinea-pigs are shown in Table 2.

Phenylephrine (selective α_1-agonist) and yohimbine (selective α_2-blocker) significantly ($P < 0.001$) potentiated the cardiotoxic effects of ouabain in guinea-pigs. Prazosin (selective α_1-blocker) and clonidine (selective α_2-agonist) significantly ($P < 0.01$) increased the doses of ouabain required to produce early arrhythmia, ventricular fibrillation and cardiac arrest. However, phenoxybenzamine (a non selective α-blocker) failed to alter the cardiotoxic effects of ouabain (Table 2).

Discussion

The relationship between the adrenergic nervous system and digitalis-induced arrhythmias is well established (Boyajy & Nash, 1968; Cagin *et al.*, 1976). Cardiac glycosides cause increased neurotransmitter overflow from autonomic nerve endings in a variety of tissues including heart (Stickney, 1980; Powis, 1983). The cardiac irregularities caused by digitalis glycosides are mediated mainly through sympathetic stimulation and the release of catecholamines (Pace & Gillis, 1976). Exclusion of sympathetic nervous system by cardiac denervation or spinal cord transection significantly increases the amount of digitalis needed to produce ventricular arrhythmias (Raines *et al.*, 1967; Cagin *et al.*, 1976). Digitalis intoxication causes non-uniform changes in activity within cardiac sympathetic nerves and these changes in the sympathetic discharge to the heart may result in the non-uniformity of electrical properties of myocardial cells (Kim *et al.*, 1984).

Lechat & Schmitt (1982) reported that clonidine, a selective agonist of presynaptic α_2-adrenoceptors, accorded protection against arrhythmogenic effects of ouabain; piperoxan, a preferential α_2-adrenoceptor antagonist, reduced the doses of ouabain required to produce ventricular arrhythmias in guinea-pigs. The results of the present study conform with the above findings. Clonidine accorded significant protection in our study and yohimbine, the selective α_2-antagonist, like piperoxan enhanced the ouabain toxicity.

Clonidine stimulates peripheral presynaptic α_2-adrenoceptors, thus causing a diminished release of noradrenaline from the nerve endings towards the

Table 1 Effect of α-adrenoceptor agonists and antagonists on blood pressure (BP) and heart rate (HR) in guinea-pigs

Drug	n	*Dose* (mg kg^{-1})	*Change in BP* (mmHg)	*Change in HR* (%)
Phenylephrine	6	5.0	+56.00 ± 11.34	−19.75 ± 1.95
Prazosin	6	2.0	−26.00 ± 2.45	−21.46 ± 2.86
Clonidine	5	0.5	− 7.75 ± 1.89	−14.82 ± 2.28
Yohimbine	6	2.0	+18.57 ± 1.43	+28.29 ± 9.55
Phenoxybenzamine	6	10.0	− 9.50 ± 2.00	−12.53 ± 3.57

Values are expressed as mean ± s.e.mean.

Table 2 Effect of α-adrenoceptor agonists and antagonists on ouabain-induced arrhythmias in guinea-pigs

Drug	n	*Dose* (mg kg^{-1})	*EA*	*VF*	*CA*
Control (saline)	14	–	15.30 ± 0.61	23.02 ± 0.98	30.54 ± 1.04
Phenylephrine	6	5.0	7.23 ± 1.19**	12.48 ± 1.29**	17.52 ± 1.32**
Prazosin	6	2.0	18.04 ± 0.48*	29.63 ± 1.62*	38.86 ± 1.29**
Clonidine	6	0.5	20.45 ± 1.40*	36.38 ± 3.43*	43.48 ± 2.79**
Yohimbine	6	2.0	10.94 ± 0.65**	17.13 ± 0.86**	22.12 ± 1.33**
Phenoxybenzamine	6	10.0	15.34 ± 0.91	24.06 ± 0.60	31.67 ± 0.98

*$P < 0.01$; **$P < 0.001$.
Values are expressed as mean ± s.e.mean of the doses of ouabain (μg 100 g^{-1} body weight) required to cause early arrhythmia (EA), ventricular fibrillation (VF) and cardiac arrest (CA).

heart and by stimulation of central α_2-adrenoceptors reduces the peripheral sympathetic tone and thus decreases the plasma catecholamines (Starke *et al.*, 1974; Cavero & Roach, 1980; Dejonge *et al.*, cited in Vanzwieten & Timmermans, 1984). The reduction of sympathetic tone and the inhibition of the release of neurotransmitters may be the contributing factor for the antiarrhythmic activity of clonidine. Gillis & Quest (1979) reported that the dose of digitalis glycosides required to produce ventricular arrhythmias is reduced by enhancing the sympathetic outflow to the heart. It is known that yohimbine increases the noradrenaline release rate (Majewski *et al.*, 1983a,b) and this probably accounted for the enhancement of ouabain cardiotoxicity in yohimbine pretreated guinea-pigs.

In the present study phenylephrine, a selective α_1-adrenoceptor agonist enhanced the cardiotoxicity of ouabain whereas prazosin a selective α_1-antagonist accorded significant protection to guinea-pigs against ouabain arrhythmias. It has been suggested that cardiac α_1-adrenoceptors may be involved in the disorders of cardiac rhythm and prazosin exerts its antiarrhythmic effect by blocking these receptors (Sheridan *et al.*, 1980). The results of the present study show that the stimulation of α-receptors helps ouabain in disrupting the cardiac rhythm while the blockade of postsynaptic α-receptors inhibits ouabain cardiotoxicity by blocking the effect of released catecholamines on the heart. Sheridan *et al.* (1980) proposed that prazosin exerts its antiarrhythmic effect by blocking α_1-adrenoceptor-mediated electrophysiological derangements.

Phenoxybenzamine a nonselective α-adrenoceptor blocker with a comparable affinity for both α_1- and α_2-adrenoceptors (Van Zwieten & Timmermans, 1984) was ineffective in altering the arrhythmogenic effects of ouabain in our study. The non-specific blockade of both subtypes of α-adrenoceptors may be the reason for its ineffectiveness.

In conclusion, it appears that the stimulation or blockade of α-adrenoceptors can alter the cardiac effects of ouabain, depending on the receptor subtype stimulated or blocked. Selective α_1-receptor stimulation and α_2-receptor blockade enhances the cardiotoxicity of ouabain while selective α_2-receptor stimulation and α_1-receptor blockade results in protection against the cardiotoxic effects of ouabain in guinea-pigs.

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