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THE ROLE OF THE LOCAL ANAESTHETIC PROPERTIES OF β-ADRENOCEPTOR BLOCKING AGENTS IN ANTAGONIZING $CaCl_2$-INDUCED ARRHYTHMIAS IN THE RAT

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1 Eight β-adrenoceptor blocking agents were compared for their ability to antagonize arrhythmias induced by bolus injections of $CaCl_2$ in rats.

2 Only those β-blockers possessing local anaesthetic properties were effective in antagonizing this type of arrhythmia and there was a highly significant correlation between antiarrhythmic and local anaesthetic properties.

3 Effects on adrenoceptors seem to play only a minor role in the genesis of this type of arrhythmia.

Introduction

$CaCl_2$ induces arrhythmias mainly through a direct action on the myocardium (Grumbach, Howard & Merril, 1954; Cuparencu, Ticsa, Csutak, Sandor, Barzu, Safta & Do Trung Dam, 1978) but also possibly through an indirect action mediated through the sympathetic nervous system (Malinow, Battle & Malamud, 1953; Papp, Forster, Szekeres & Rossler, 1966). Although propranolol has been shown to antagonize arrhythmias induced by bolus injection of $CaCl_2$ in rats (Papp *et al.*, 1966), other β-adrenoceptor blocking agents have apparently failed to antagonize arrhythmias induced by slow intravenous infusion of $CaCl_2$ in dogs (Cuparencu *et al.*, 1978). It therefore appeared worthwhile to investigate to what extent these discrepancies could be explained in terms of differences between local anaesthetic and specific β-adrenoceptor blocking properties of these substances.

Methods

Antagonism toward $CaCl_2$-induced arrhythmias

Male albino rats, Wistar-Morini strain, weighing 350–400 g were anaesthetized with intraperitoneal urethane (1 g/kg). Arrhythmias were produced and scored according to the method of Grimaldi, Maggi & Meli (1981). Each β-blocker was administered intravenously at several dose levels; six or more animals were used at each dose level.

Local anaesthetic properties

These were assessed according to Bianchi (1956). Each β-blocker was tested at several dose levels (40 mice per dose). In view of the slight local anaesthetic properties of some β-blockers, the % concentration that was effective in 30% of the animals (EC_{30}) was determined.

β-Adrenoceptor blocking properties

Male albino rats, Wistar-Morini strain, weighing 350–400 g received intraperitoneal sodium barbitone (200 mg/kg). The right carotid artery and left jugular vein were cannulated for blood pressure recording and drug injection respectively. The blood pressure signal was used to trigger a cardiotachometer and heart rate recorded accordingly. Isoprenaline was administered at a dose of 0.15 μg/kg and the resultant tachycardia recorded 1 min after drug treatment. Each β-blocker was administered intravenously at several dose levels (3 or more animals per dose).

Statistical analysis

The mean effective dose (ED_{50}) for β-adrenoceptor blocking and antiarrhythmic properties, as well as the concentration producing local anaesthetic effects in 30% of the animals (EC_{30}), and their 95% confidence limits were calculated according to Litchfield & Wilcoxon (1949). The linear regression was calculated according to the method of least squares.

Drugs

The following drugs were used: (±)-isoprenaline hydrochloride (Serva), reserpine base (Gianni), (−)-adrenaline base (Merck), $CaCl_2$, $2H_2O$ (MSD), propranolol base (ICI), alprenolol base (Byk Gul-

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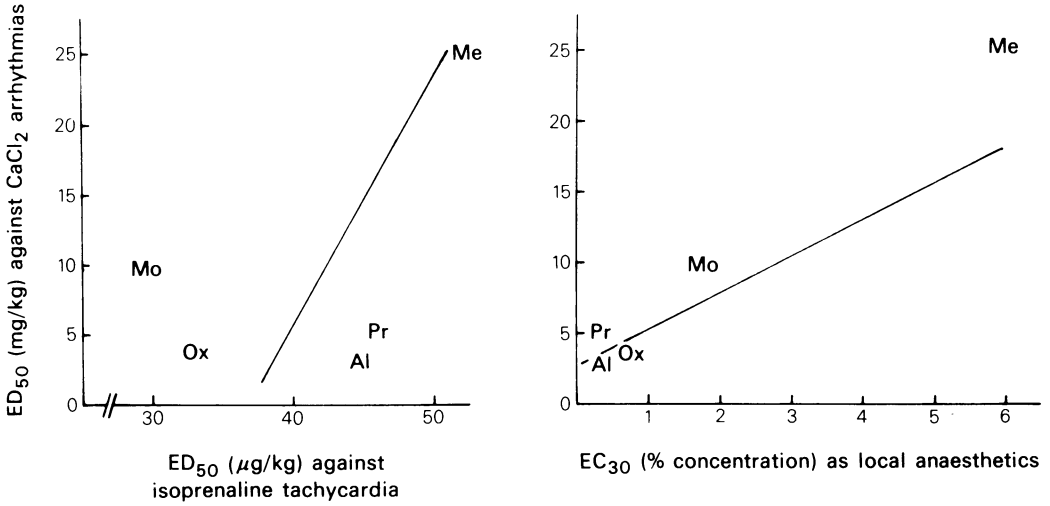

Figure 1 Correlation between β-adrenoceptor blocking and anti-arrhythmic properties (a) and between local anaesthetic and anti-arrhythmic properties (b).
Al = alprenolol; Me = metoprolol; Mo = moprolol; Ox = oxprenolol and Pr = propranolol. In both (a) and (b), $n = 5$; in (a) $r = 0.3632$ and P = not significant; in (b) $r = 0.9526$ and $P < 0.01$.

den), oxprenolol base (Ciga-Geigy), metoprolol base (Ciba-Geigy), moprolol HCl (Simes), practolol base (ICI), atenolol base (ICI) and sotalol base (Bristol). All bases (with exception of metoprolol which was injected as the tartrate) were solubilized by addition of stoichiometric amounts of HCl.

Results

Among the β-blockers tested, only propranolol, alprenolol, oxprenolol, metoprolol and moprolol effectively antagonized $CaCl_2$-induced arrhythmias in a dose-dependent manner and only these compounds possessed significant local anaesthetic activity. There was a highly significant correlation between this property and antagonism of $CaCl_2$-induced arrhythmias (Figure 1). On the other hand, atenolol, practolol and sotalol failed to antagonize arrhythmias at doses as high as 60 mg/kg or to exert local anaesthetic activity in a concentration as high as 6%. All the β-blockers tested antagonized isoprenaline-induced tachycardia in a dose-dependent manner. There was no correlation between this property and antagonism of $CaCl_2$-induced arrhythmias (Figure 1).

Discussion

It is widely accepted that hyperactivity of the sympathetic nervous system plays a significant role in the genesis of certain cardiac arrhythmias (Singh & Jewitt, 1974) and that β-adrenoceptor blocking drugs protect animals against various disturbances of cardiac rhythm (Hauswirth & Singh, 1979). The observation that (+)- and (−)- isomers of some β-blockers were equally effective against certain experimental arrhythmias, even though the (+)-isomers are largely devoid of β-adrenoceptor blocking properties (Somani & Lum, 1964; Lucchesi, 1965; Parmley & Braunwald, 1967; Apantaku, Baumgarten & Ten Eick, 1975), raises the question as to whether antiarrhythmic effectiveness is due to specific β-adrenoceptor blockade, local anaesthetic properties or both, (Dohadwalla, Freedberg & Vaughan-Williams, 1969; Singh & Vaughan-Williams, 1970). Recent investigations support the view that, when given in therapeutic doses, the antiarrhythmic properties of β-blocking drugs are mainly, if not solely, due to effects at β-adrenoceptors (Singh & Jewitt, 1974; Vaughan-Williams, 1975; Hauswirth & Singh, 1979). Experimental evidence for this view could be inferred from the observation (Cuparencu *et al.*, 1978), that only potent β-blockers such as propranolol and oxprenolol effectively antagonized arrhythmias induced by slow intravenous infusion of $CaCl_2$ in the dog, whilst sotalol and practolol did not. On the other hand, the observation that only β-blockers possessing local anaesthetic (quinidine-like) properties (class 1 antiarrhythmics; Vaughan-Williams, 1970) were effective in our experimental conditions, argues

against a primary role of β-adrenoceptors in the genesis of arrhythmias induced by $CaCl_2$ in the rat. This viewpoint is substantiated by a previous finding that reserpine, in doses that produced catecholamine depletion at cardiac level, slightly antagonized arrhythmias produced under similar experimental conditions (Papp *et al.*, 1966). It is not our aim to revive the controversy on the mechanism responsible for the antiarrhythmic action of β-blockers in man. Rather, we wish to stress the fact that different mechanisms may be responsible for the genesis of this type of arrhythmia depending upon the method of induction and/or the animal species studied.

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