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Alpha-Adrenergic Blockers on Ventricular Automatism in Rat Heart

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The role of the alpha-adrenergic receptors in the genesis of cardiac arrhythmias induced in the isolated rat right ventricle has been studied. The administration of six alpha-adrenergic blocking agents (phenoxybenzamine, dibenamine, phentolamine, tolazoline, azapetine and SY-28) did not alter the automatism induced. Even when can not be excluded the existance of alpha-adrenergic receptors in the rat ventricle, it is clear that alpha-blocking drugs are ineffective to abolish the arrhythmias induced by an increase in the activity of the Purkinje fibers.

It is widely accepted the hypothesis for the existance of only beta-adrenergic receptors in the myocardium (10). Recently, evidence has been presented to support the presence of alpha-adrenergic receptors in the myocardium (1, 2, 7, 8, 12). Moreover, VARGAFTTIG and COIGNET (11) reported that phentolamine delayed the appearance of aconitine arrhythmias in the rat and blocked the ventricular fibrillation caused by chloroform inhalation in the mice, while GOULD and RAMANA REDDY (6) propose that phetolamine can supress ventricular and supraventricular premature beats in the man. With these results in mind, we have tested in this paper the antiarrhythmic effects of six alpha-adrenergic blocking agents on the automatism induced in the rat right ventricle.

Materials and Methods

Sprague-Dawley rats of either sex, weighing 250-300 g were used throughout. The animals were killed by a blow on the head and the right ventricle was isolated and mounted on platinum electrodes. The experimental procedure to produce automatism in the isolated hight ventricle of the rat and to assess the antiarrhythmic activity of drugs in this model has been

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described in detail in a previous paper by GARCÍA DE JALÓN *et al.* (5).

The following drugs were tested: isoprenaline hydrochloride (Aleudrine, C.H. Boehringer & Sohn), regitine hydrochloride (Ciba), phenoxybenzamine hydrochloride (Dibenzyline, Smith, Kline & French), dibenamine hydrochloride (C.H. Boehringer & Sohn), azapetine phosphate (Ilidar, Hoffman La Roche), tolazoline hydrochloride (Priscol, Ciba) and SY-28 (Parke Davis).

Results

When the isolated right ventricle of the rat was exposed to isoprenaline (10^{-6} M) plus high frequency of stimulation (10 Hz, for 5 sec.) ventricular automatism usually appeared wich tended to persist unless treated (5).

When the ventricular muscle is contracting maximally under the positive inotropic effect of isoprenaline, a shock of high frequency stimulation (10 Hz) breaks the myocardium adaptive capacity for maintaining equilibrium between oxygen supply and demand. Such imbalance is greater in the ventricular muscle as compared to atrial muscle because of the greater thickness of the muscle wall of the former.

The six alpha-adrenergic blockers were used in a range of concentrations between 5×10^{-7} and 1×10^{-4} M. The highest concentration was set at 10^{-4} M in order

Table I. *Effect of alpha-adrenergic blocking drugs on cardiac arrhythmias in the rat ventricle.*

Drug (10^{-4} M)	Total number of automatism suppression: Total number of experiments	Protection degree *
Phenoxybenzamine	0/15	—
Dibenamine	3/19	1
Phentolamine	1/20	4
Tolazoline	1/18	4
Azapetine	3/22	4
SY-28	0/15	—

* Protective effects were scored from 0 to 4 according to García de Jalón et al. (5).

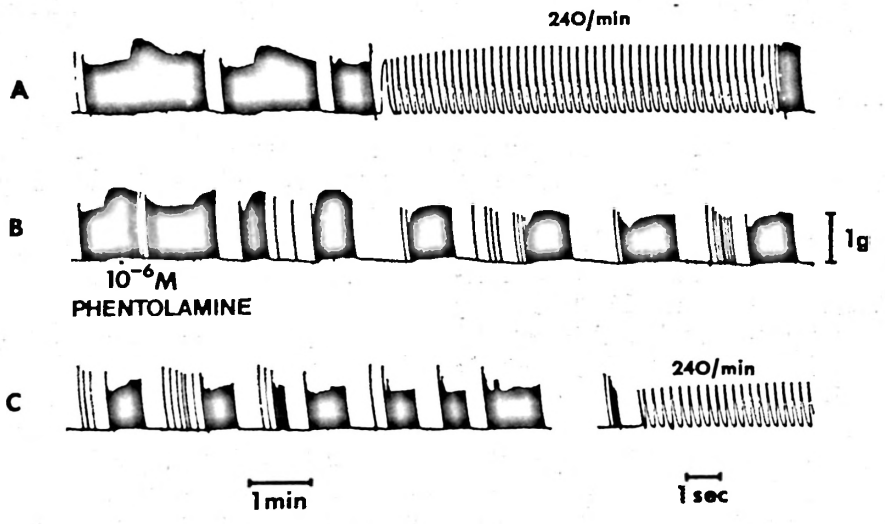

Fig. 1. *Effect of phentolamine on ventricular automatism in the rat ventricle.* In A, volleys of automatism at a frequency of 240 betas/min were induced. In B, phentolamine (10^{-4} M) was added, but no significant changes were observed both in the type or in the frequency of the discharges (panel C).

to exclude unspecific interactions. None of the drugs tested was able to abolish the ventricular automatism induced, in a total of 109 experiments performed (table I). Even with a concentration as high as 1×10^{-4} M, which in some experiments produced a depression in myocardial contractility, the automatism continued indisturbed. A typical experiment is illustrated in figure 1. Only in those experiments (not included in the table) performed with concentrations above 10^{-4} M, the automatism was abolished. Such a high concentrations produced a great depression in the preparation conferred by the antiarrhythmic effect of the alpha-blocking agents. In these experiments the contractility was so depressed that the voltaje had to be increased twentyfold to obtain some contractile response that nevertheless diminished steadily within a short time. A positive chronotropic effect was observed in four experiments following the administration of phentolamine or tolazoline (10^{-5} M-3×10^{-5} M).

Discussion

The possible existence of alpha-adrenergic receptors in the myocardium reappears when WENZEL and SU (12) reported that the negative inotropic effect induced by norepinephrine in the rat ventricle was specifically blocked by phenoxybenzamine but no by beta-adrenergic blockers. Similar results were found by BENFEY and VARMA (1) in the rabbit auricle and by GOVIER (7) in the guinea pig auricle. GOVIER (8) reported that the increase in the refractory period (RP) induced by epinephrine and phenylephrine in the guinea pig atria could be blocked by phenoxybenzamine and BERGER and MOCKLER (2) demonstrated that the effect of quinidine on the RP of the rat heart increased 165 and 195 % by phenoxybenzamine and phentolamine, respectively, in relation to quinidine-treated hearts.

The results presented in this paper appears to minimize the direct myocardial effect postulated to explain the antiarrhythmic action of the alpha-blocking drugs. In fact none of the six drugs used was able to abolish the chronotropic responses induced by our experimental procedure when they were used at concentrations enough to block the activation of alpha-adrenergic receptors in the smooth muscle. This results could be explained if the automatic activity of the Purkinje fibers was mediated through beta-adrenergic receptors but not through alpha. The positive chronotropic effect observed with phentolamine and tolazoline has been explained by FURCHGOTT (4) as due to a partial agonistic action of both drugs. Recently has been postulated that norepinephrine regulates its own release through a negative feed-back mechanism mediated by prejunctional alpha-adrenergic receptors (9). According to this idea the positive chronotropic effect observed in some experiments with phentolamine and tolazoline could be due to an increased release of norepinephrine in the myocardium.

Even when the ventricular automatism was firstly induced by isoprenaline, its persistance may be due to another factors unrelated with sympathomimetic effects. The alpha-blocking agents have many other pharmacological properties which probably can play an important role in the myocardial depression observed at higher concentrations. Benzodioxans and haloalkylamines are known to be several times as potent as quinidine in depressing the myocardium (3). However, neither this quinidine-like effect not their atropinic or local anesthetic properties were enough to suppress the ventricular automatism.

From these results can not be excluded the existance of alpha-adrenergic receptors in the rat right ventricle but they give evidence that alpha-blocking agents are ineffective in abolishing the automatism induced in this preparation by an increase in the activity of the Purkinje fibers.

Resumen

Se estudia el posible papel de los receptores alfa-adrenérgicos en la génesis de las arritmias desencadenadas en el ventrículo derecho aislado de rata. La administración de seis bloqueantes alfa-adrenérgicos (fenoxibenzamina, dibenamina, fentolamina, tolazolina, azapetina y SY-28) no modifica de forma significativa el automatismo inducido. Aunque no se puede descartar la posible existencia de receptores alfa en el ventrículo de rata, queda patente que los bloqueantes alfa-adrenérgicos utilizados no abolen el automatismo provocado por un aumento de actividad de las fibras de Purkinje.

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